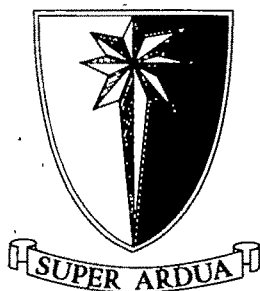


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- 1 Thomas EJ, Cooke ID. *British Medical Journal* 1987; 294: 272-274
- 2 UK Multicentre Study. Data on file



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The journal has published check lists to guide contributors preparing accounts of certain types of research. These appeared in 1989 (Vol 96): Bracken M. B., Reporting observational studies, 383–388; Wald N. & Cuckle H., Reporting the assessment of screening and diagnostic tests, 389–396; Grant A., Reporting controlled trials, 397–400.

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- (2) The use of confidence intervals is encouraged.
- (3) The symbol $\pm$ should not be used when presenting SE or SD. Presentation such as 'the mean was 14.2 (SD 3.2) mg' is preferred.
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COMMENTARIES

Quality of the perinatal autopsy

The article of medical faith that a high autopsy rate is a measure of good clinical practice carries the unspoken assumption that the sophistication of pathologists in investigating patients after death will increase in line with that of their clinical colleagues in investigating patients in life. In fact the opposite may be the case. Structural pathologists now prefer to be called histopathologists rather than morbid anatomists, have become enamoured of methods of investigation such as immunocytochemistry, electron-microscopy and *in situ* DNA hybridization, and may be reluctant to desert their laboratories for a visit to the mortuary. When they do so they may lack the gross observational skills of their predecessors. There is seldom the drive to investigate the deceased patient of any age with the enthusiasm and technical armamentarium that is directed towards the interesting tumour.

This deficiency is highlighted in relation to the perinatal autopsy by the advances in prenatal diagnosis and clinical genetics which now pose precise questions on causation and recurrence risks to the histopathologist. Too often the response is a hurried and meaningless ritual by an uninterested pathologist that leaves the clinician feeling embarrassed that he requested permission from the parents for such an unproductive mutilation of their deceased infant.

Dr Rushton in this issue of the journal (p. 624) has now attempted a quantitative assessment of the adequacy of perinatal postmortem examinations in the West Midlands, as judged by the postmortem report. Scores were assigned according to the number of the standard textbook procedures for perinatal autopsy that had been carried out and recorded. These included simple body measurements, weights of organs, histological examination of tissues and ancillary studies such as radiology and microbiology. Only 12.5% of the possible maximum score was devoted to 'descriptive content' so that the exer-

cise measured procedural adequacy rather than observational skill or diagnostic ability. The survey revealed that half the autopsies performed outside the regional centre were procedurally inadequate, even on the low standard set. Particularly depressing was the lack of histology performed on many of these cases and the willingness of 'histopathologists' to make diagnoses of bronchopneumonia and hyaline membrane disease without histological confirmation. This could be seen as mere ignorance of the value of a full examination of these small or macerated infants or, perhaps, as a subconscious rejection of the perinatal autopsy as a subject worthy of examination by the procedures the pathologist uses in his routine work. It cannot be explained by lack of local facilities for this basic form of pathological study.

There is a tendency for pathologists to underperform in those areas where they feel unsure of their knowledge or ability. Thus I find that registrars, when being trained in perinatal autopsy technique, may weigh the fetal brain but make no other comment on its gross appearance, either before or after fixation. This seems to be due to the belief that brains can only be examined by those with special training in neuropathology. Yet comments on relative maturity of convolutional pattern, softness, pallor or congestion of cerebral substance or the approximate location and nature of gross lesions, are within the capability of any pathologist or indeed any medical practitioner.

This phenomenon was recognized by Rushton in the finding that the only cerebral lesion recorded was intraventricular haemorrhage, although other forms of cerebral damage are common in the perinatal period.

The increasing tendency for clinicians to refer cases to a regional centre for examination by a paediatric or perinatal pathologist is understandable, given the unsatisfactory nature of many perinatal autopsies performed at district

general hospitals. In the North West Thames Region over 200 fetal and infant deaths are now referred annually to the regional centre at Hammersmith for examination directly from outside hospitals.

It is important to make the point that in each region there are a number of district general hospital (DGH) pathologists willing and interested to perform good fetal and perinatal autopsies, despite a heavy work load in surgical pathology. They should certainly be encouraged to carry on with the work as it is unrealistic and undesirable to expect all fetal and neonatal deaths to be transferred to a regional centre many miles away for postmortem examination. The levels of funding and staffing of regional perinatal and paediatric pathology centres is such that they could not in any event handle the referral of all cases within their regions. The regional specialist perinatal pathologist can help the DGH pathologist by providing short periods of training in the specialist department, advice by telephone on procedures, or consultation on specific areas of organ pathology such as neuropathology or cardiac anomalies, in addition to accepting complex cases for referral. This role of training and support is fully endorsed in the report by the RCPATH Working Party (1990) on paediatric and perinatal pathology. In addition it may be pointed out that a range of texts has become available in the last few years to help the histopathologist in this area of study (Wigglesworth 1984; Keeling 1987; Reed *et al.* 1989; Wigglesworth & Singer 1991).

One problem which may well contribute to inadequate postmortem examination is the consistent and gross underpricing of the procedure. Rushton suggests that the true cost of a postmortem, including adequate ancillary investigations, may be as high as £600–£1000, although he does not provide a breakdown of the relevant costs. The only postmortem costing currently available is the fee negotiated by the BMA for coroner's work. The fee currently paid by the coroner to a consultant pathologist for performing an autopsy is £53.80. This is of the same order as the cost to a householder of a simple repair to a washing machine. Even if payment for 'a special examination' (i.e., one that includes histology and/or other investigations) is authorized at a cost of £150.30 this would not realistically cover the cost of a full set of investigations such as radiology and cytogenetic and virological studies. The sums may be appro-

priate as honoraria to a salaried pathologist, but lead to the erroneous but widespread belief that the procedure is simple and cheap, a belief which may have a self-fulfilling effect. When true cost calculations are made they may come as a shock to both the coroner's service and health authorities.

If contracts are to be placed in future for fetal and perinatal postmortems it will be essential to draw up quality standards so that health authorities will know precisely what they are buying. There should be standards for the skills or level of supervision of the prosector, details of measurements and weights to be recorded routinely, details of organ sampling for histology to be undertaken, details of ancillary procedures, such as photography, radiology, microbiology and cytogenetics that are available, and when they will be utilized, and details of rapidity of provision of initial and final reports. Minimum standards along these lines were set out by the Joint Working Party (1988), which was set up following an assessment by an RCOG subcommittee of a national sample of perinatal autopsy reports using similar criteria to those of Rushton's study.

The standards agreed for an autopsy at a DGH may be less comprehensive than those for the regional centre and the price may be correspondingly lower. Since many cases do not require the level of ancillary investigation available at the regional centre, an authority may elect to purchase a proportion of their pathological services locally and a proportion at the regional centre. The situation is analogous to that involved in care of ill newborn infants, of whom some may be cared for in the local special care baby unit and some may need referral to a neonatal intensive care unit.

The need to prepare and adhere to defined standards of perinatal autopsy practice should increase the awareness of what can be involved in a good perinatal postmortem examination and should have a powerful effect in ensuring that health authorities get the services which their patients require for proper counselling after loss of a fetus or infant.

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Management of tubal infertility in the 1990s

Tubo-peritoneal damage is found in about 20% of couples investigated for infertility (Hull *et al.* 1985) and accounts for more than 40% of female infertility. In the last 2 decades microsurgical techniques have greatly improved the chances of pregnancy for these patients.

Success rates have been particularly promising in patients suffering from proximal tubal occlusion with reported livebirth rates of 40 to 60%. (Diamond 1979; Winston 1980a; Gomel 1983; Donnez & Casanas-Roux 1986a; Lavy *et al.* 1986; McComb 1986; Patton *et al.* 1987); and in patients with fimbrial conglutination, encapsulation or phimosis, where fimbrioplasty procedures have resulted in intrauterine pregnancy rates of the same order (Bateman *et al.* 1987; Lavy *et al.* 1987; Cohen 1988). Good results have also been achieved in the reversal of sterilization, with conception rates of 60 to 80% and failure mainly associated with particularly destructive sterilization techniques and excessive tubal shortening (Rock *et al.* 1987; Sotrel 1990).

However, the commonest site of tubal occlusion is at the fimbrial end and the role of salpingostomy in the management of distal tubal occlusion has recently been questioned by Watson *et al.* (1990) who found only two livebirths in a series of 40 patients operated on by general gynaecologists.

Most cases of distal tubal occlusion are due to ascending genital tract infection and so the incidence is affected by parity, sexual mores, social,

cultural and religious factors. Other causes include endometriosis, iatrogenic factors (Darling 1982) and pelvic peritonitis, most often secondary to perforated appendicitis (Powley 1965), and in these patients endosalpingeal damage is usually less severe with a correspondingly better prognosis from surgery.

Before the advent of microsurgery, salpingostomy for the correction of hydrosalpinx had little success, with livebirths in the region of 5% (Sieglar 1969). The introduction of microsurgical techniques (Winston 1980b), of which use of the operating microscope is only one aspect, has greatly improved results (Swolin 1975; Gomel 1978; Siegler & Kontopoulos 1979; Winston 1980a; Garcia & Mastroianni 1980; Verhoeven *et al.* 1983). Sotrel (1990) has analysed 16 series of microsurgical salpingostomy published since 1980. Pooled results of this nature are difficult to assess: different populations, selection criteria, surgical techniques, adjuvant therapies, follow-up and analysis techniques make comparisons difficult. Nevertheless, a remarkable degree of uniformity emerges. Altogether 1728 patients had 26% intrauterine and 8.3% ectopic pregnancies.

There is general agreement that results from salpingostomies depend on the degree of tubal damage and the extent and nature of the commonly associated adhesions (Gomel 1983). These have been graded in order of severity and, when done retrospectively, clear correlation is found between the extent of the pathology and

the outcome of surgical repair. Rock *et al.* (1978) classified 99 patients who underwent salpingostomy as having mild, moderate or severe disease, based on the size of the hydrosalpinges, condition of the fimbriae, extent of the adhesions and rugal pattern on the pre-operative hysterosalpingogram. Of these 99 patients, 15% had mild disease with an 86% pregnancy rate; 34% had moderate disease with a 26% pregnancy rate and 51% had severe disease with an 8% pregnancy rate. Other classifications were proposed by Hulka (1982) and Levinson (1983).

Subsequently, grading has been used for pre-operative prognosis (Boer-Meisel *et al.* 1986; Donnez & Casanas-Roux 1986b; Mage *et al.* 1986) and the American Fertility Society (1988) has devised a scoring system based on the extent of ampullary dilatation, thickness and rigidity of the tubal wall, condition of the endosalpinx and extent and nature of the adhesions, and has recommended *in-vitro* fertilization for patients with a poor prognosis. Of these classifications, that proposed by Boer-Meisel *et al.* (1986) is the simplest and most practical: of their 108 patients, 25% were in group I and had a 59% term pregnancy rate; the 40% in group II had a 16% term pregnancy rate, whilst in the remaining 35% in group III, the term pregnancy rate was only 3%. The recent introduction of trans-laparoscopic salpinogscopy (Brosens *et al.* 1987; Shapiro *et al.* 1988) will help to define even further patients who can expect a good prognosis, and reduced ectopic pregnancy rate, from surgery.

Apart from the extent of tubo-peritoneal damage, two other factors are important in the prognosis for the surgical management of distal occlusion.

Female fecundability decreases after the age of 30 and more markedly after 35 (Guttmacher 1952; CECOS 1982; Gindoff & Jewelewicz 1986). Surgical treatment of infertility gives a declining success rate in women over 35 (Malone & Ingersoll 1968). Apart from decreased conception rates, the higher miscarriage rate in women over 35 is a serious problem (Jansen 1982). Experience with IVF has shown a similar decline in livebirths to women over 35 (Edwards *et al.* 1984; Steptoe *et al.* 1986; Romeu *et al.* 1987) and in women over 40, multiple attempts at IVF do not appear to improve the pregnancy outcome.

The other factor influencing pregnancy rates after surgery is the length of follow-up. More

than 60% of patients who achieve intrauterine pregnancy after salpingostomy do so after the first post-operative year (Gomel 1983; Russell *et al.* 1986). It has been suggested that this long surgery to conception interval is due to time taken by the endosalpinx to recover after relief from the hydrostatic pressure caused by the hydrosalpinx, but there is little real evidence for this, and the long delay may merely be a manifestation of lowered fecundability in these patients, or may even be a result of the second look laparoscopy and hydrotubation often performed in those who have not conceived within a certain time of surgery.

Lilford & Watson (1990) have suggested that there is no further place for open surgery to reconstruct tubes with distal occlusion; that laparoscopic salpingostomy should be attempted at the time of the preliminary diagnostic laparoscopy and if this is impossible or unsuccessful, the most cost effective management is referral for IVF.

Gomel (1977) first described nine laparoscopic salpingostomies, but found the technique unsatisfactory when the tube was adherent to the pouch of Douglas or the lateral pelvic wall. Further series were published by Mettler *et al.* (1979), Favez (1983) and others, but the numbers were small and the necessary adhesiolysis limited success. More recently laser laparoscopy has been used to overcome this problem (Daniel & Herbert 1984; Daniel *et al.* 1986; Donnez & Nisolle 1989; Daniel 1989). The results are not better than those from open surgery. Complications from laparoscopy are more frequent than from laparotomy and, in the case of laser laparoscopy, special precautions have to be taken to protect surgeons and theatre staff. The technique is time consuming and the expensive equipment has added to the cost of treatment. In this issue of the Journal (p. 637) Winston & Margara believe that the rate of re-occlusion is higher. As yet there has been no randomized study comparing the two techniques, but it seems unlikely that laparoscopic surgery will replace open surgery except in the hands of a few enthusiasts when used for fimbrioplasty or the most favourable cases of hydrosalpinx.

Livebirth rates following IVF are still disappointingly low. However, the usually quoted 9–10% livebirth rates per treatment cycle (Medical Research International 1989; Interim Licensing Authority 1990) do not give a true picture as results in tubal infertility patients are bet-

ter than the overall results (Mahadevan *et al.* 1983; Steptoe *et al.* 1986) and better units achieve better results.

Yet, even if a livebirth rate of 25% per stimulation cycle or a cumulative pregnancy rate of 40% after three treatment cycles (Guzick 1986) is achieved by IVF in these women, the overall outlook would not be improved by indiscriminate referral for IVF-ET. Furthermore, such calculations pay no attention to the complications of IVF, of which hyperstimulation and multiple pregnancy are the commonest, or the high perinatal mortality of 26/1000, three times the national average (ILA 1990) resulting from the large numbers of preterm births.

Lilford & Watson (1990) have calculated the cost per baby following salpingostomy as £20 000 on the assumption that the livebirth rate is only 5%. However, this drops to £5000 assuming even a modest 20% livebirth rate from salpingostomy and takes no account of subsequent births which at least half these patients experience without further treatment. Moreover, few surgeons hospitalize their patients for as long as 10 days on which their calculations are based.

Costings for IVF range from £8800 per baby (Page 1989) to US\$50 000 (Wagner & St Clair 1989), but these figures pay insufficient attention to the hidden costs of IVF babies resulting from the high cost of caring for preterm babies, or the caesarean section rate of nearly 50% (ILA 1990) in women delivered following IVF.

In this issue there are two articles on the outcome of microsurgical salpingostomy. Winston & Margara (p. 637) analyse results of 388 patients they treated for distal tubal occlusion. Sixty-five of these had had previous failed surgery. This is the largest series of salpingostomies reported. Overall 22% had one term pregnancy, and more than half had at least one further delivery. Of their patients, 291 were graded according to a modified Boer-Meisel classification: of these 209, classified as stage I or II, had 57 (27%) term pregnancies, whilst the remaining 82 patients, graded stage III and IV, had 6 (7%) term pregnancies. Detailed selection criteria are not given, but patients with severe cornual damage or bipolar blockage were excluded.

Singhal *et al.* (this issue p. 628) from Sheffield report 232 tubal procedures of which 97 were salpingostomies. In this subgroup 29% had one or more livebirths, with a cumulative conception rate of 40% at the end of 3 years. Patients were

unselected and the authors conclude that hydro-salpinges greater than 20 mm, bipolar occlusions and extensive adhesions were significant adverse factors.

Perhaps the most significant feature of these reports is that they emanate from units where outstanding IVF facilities are also available and bias in recommending one or the other form of treatment to patients is therefore reduced to a minimum.

So what advice should be given to patients with bilateral distal occlusion?

It has to be stated that at the present time many infertile couples do not have access to the full range of diagnostic or therapeutic services. Whether patients with tubal infertility are referred for surgery or IVF often depends on the local availability of services and on who does the referring. The latter may be done by infertility specialists, general gynaecologists, general practitioners, or by self referral, often influenced by advice from non-professional friends or even the media. Financial considerations may influence the method of treatment sought. Funding for IVF from NHS resources is totally inadequate so that often 'selection' for surgery or IVF depends more on the patient's financial status than on clinical indications. Yet, ideally, IVF facilities should be available in NHS units which also provide all other forms of treatment, including microsurgery, so that unbiased advice can be given.

The Report of the RCOG Working Party on Further Specialization in Obstetrics and Gynaecology (1982) has made specific recommendations for training of specialists in reproductive medicine (including training in tubal microsurgery) and the establishment of 24 subspecialists. Training posts for microsurgery are too few and implementation of the recommendations should be a matter of urgency.

It is to be hoped that the RCOG and the British Fertility Society will jointly recommend generally acceptable classifications of tubal disease and selection criteria for the different therapeutic methods. Multicentre trials on adjuvant therapy in tubal surgery should be arranged. Uniform follow-up methods and classification of results are required.

Ultimately such 'conscientious evaluation' of results will enable patients to be offered the treatment most suitable for their particular clinical problem. In the case of distal tubal occlusion, patients under the age of 36 with mild or moder-

ate disease should be treated in specialist centres practising microsurgery. Such treatments should be offered to those over 36 only if the disease is mild. Those rejected for surgery, together with those who have re-occlusion, have failed to conceive within 2 years of surgery, or have had an ectopic pregnancy after microsurgery, should be referred for IVF as soon as possible. The two techniques should not be regarded as confrontational, but as complementary. It is our duty as gynaecologists to exercise more conscientious selection so that patients can be directed towards that form of treatment which will give them the best chance of a livebirth.

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West Midlands perinatal mortality survey, 1987. An audit of 300 perinatal autopsies

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Summary. As part of the West Midlands regional perinatal mortality survey an audit of perinatal autopsies was performed in 10 of 20 districts in the region. Autopsy reports were available from 300 of the 426 deaths (70%) reported in these districts. These were coded for 8 aspects including the clinical summary, body measurements, descriptive content, organ weights, post mortem radiology and microbiology, histology and other relevant investigations e.g., biochemistry, cytogenetics. Overall 44% of the autopsies failed to attain an arbitrary minimum score of 300, the mean score being 299. Excluding those autopsies performed at the regional centre these figures were 50% and 268 respectively. These data indicate that a high autopsy rate does not necessarily reflect a high quality of service and further emphasise the concerns that have been expressed by obstetricians, paediatricians, geneticists, parents and parliamentarians about the perinatal pathology services in the United Kingdom.

There is increasing emphasis on audit and quality assurance in current medical practice. Since death is a clearly defined outcome, a major component in the audit of clinical practice has been the autopsy, though during the last 40 years the autopsy rate has declined dramatically to a level that many consider unacceptable (Anderson *et al.* 1989; Favara *et al.* 1989; Harrison & Hourihane 1989).

As a result efforts have been made to increase the awareness of the potential benefits that may accrue from post mortem examination (Favara *et al.* 1989) among clinicians and, in some countries, other health workers and relatives of the deceased. An increase in autopsy rates would be a vindication of such efforts, although that would only be of benefit if the standard of

the examination were high; indeed inadequate and uninformative autopsy reports have been one of the factors thought to be responsible for the current decline in autopsies (Harrison & Hourihane 1989).

Although pathologists have been involved in the audit of clinical practice they have not assessed the value of the autopsy data they provide for clinical audit. Perinatal autopsy rates have generally exceeded those in adults but in many obstetric units they have fallen below acceptable levels (Favara *et al.* 1989). Much concern has been expressed about the adequacy of such examinations, not only by obstetricians, paediatricians and pathologists, but also by parliamentarians and parental pressure groups. There is much anecdotal evidence of inadequate autopsies but few hard data are available, the only regular review of autopsy reports being that of the Confidential Enquiry into Maternal Deaths (Department of Health 1989). The value of the properly conducted perinatal and fetal autopsy cannot be disputed (Gau 1977, Duley 1986; Opitz 1987; Wigglesworth 1987; Favara *et*

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al. 1989; Russell & Berry 1989; Shen-Schwarz *et al.* 1989; Clayton-Smith *et al.* 1990). As part of the West Midlands regional perinatal mortality survey (WMRPMs) it has been possible to assess the quality of perinatal autopsies in 10 of the 20 health districts in the region.

Method

The data presented are derived from 1987, the first year of the WMRPMs. The size of the region necessitated division into two groups of health districts (A and B), the division being by ranked standardized perinatal mortality ratios (SPMR). The group A districts, which had higher SPMRs, underwent a detailed confidential enquiry into each death, while only a minimum data schedule was completed in the group B districts. Copies of the autopsy reports were sought from all deaths, and they have been analysed for the group A districts.

The reports were scored for eight factors derived from the report on fetal and perinatal pathology published by the Joint Working Party, Royal College of Obstetricians and Gynaecologists and the Royal College of Pathologists (1988), using a modification of a scheme devised by Wigglesworth (personal communication).

These factors were (total possible score allocated in brackets: (a) Clinical summary/structured autopsy request (100); (b) Body measurements: crown rump or crown heel (25), head circumference (25), foot length (25), all (100). (c) Descriptive content of autopsy (up to 100). (d) Organ weights, lungs, heart and brain (50), others in addition (50). (e) Radiology (100). (f) Microbiology (100). (g) Histology lung (50), others in addition (50). (h) Other e.g., biochemistry, cytogenetics etc. (100).

The maximum score for each factor was 100, and thus the maximum autopsy score was 800.

A total autopsy score was also calculated for

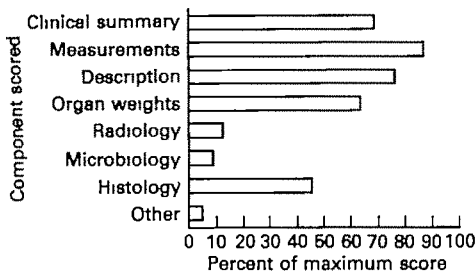


Fig. 1. Percentage maximum scores for each component scored.

each autopsy. Only seven factors were included in the score since the clinical summary, though of vital importance in assessing the final opinion, is not part of the autopsy examination. With the exception of the descriptive content of the autopsy, the remaining factors were determined on non-subjective data, and should therefore be reproducible between centres and over periods of time, thus allowing comparisons. An arbitrary minimum score of 300 was considered to be acceptable though this would not be accepted in specialist centres.

Results

A total of 882 deaths was reported to the audit, 397 stillbirths, 377 neonatal deaths and 108 miscarriages and abortions over 500 g birthweight. Overall, 609 autopsies (69%) were performed (78.6% among stillbirths, 60.7% among neonatal deaths).

Overall 846 deaths were of West Midlands residents, and of these 426 were from group A districts. Autopsy reports were available from 300 (70.4%) of these 426 deaths.

The percentage of the theoretical maximum score for each component of the autopsy assessment is illustrated in Fig. 1.

Body measurements were recorded best (87% of maximum score) while special techniques such as radiology, microbiology and miscellaneous examinations each scored <15% maximum score. Of particular note is that the histology score was <50% of the possible maximum score.

The mean total score was 299 and 44% of autopsies failed to attain the minimum score of 300 (Fig. 2). If those autopsies from group A patients performed at the regional centre are excluded, the percentage failing to attain the minimum score rises to 50% and the mean score falls to 268.

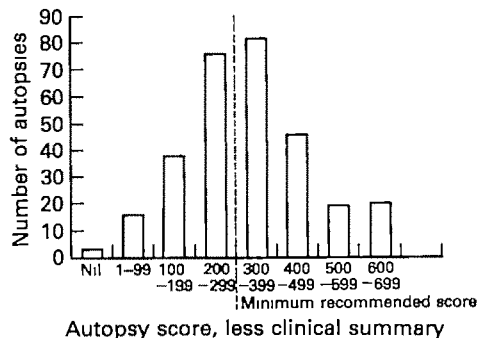


Fig. 2. Distribution of autopsy scores.

Discussion

Although the overall autopsy rate in this study falls short of the RCOG/RCPATH minimum recommended level of 75% (Joint Working Party 1988), it is much higher than most adult autopsy rates (Anderson *et al.* 1989).

However, just under half of the autopsies performed failed to attain the minimum score, which in itself may be considered to have been set too low. If these findings are reflected in group B districts and in other parts of the country, then the concerns that have been expressed about perinatal pathology services are well founded. Any complacency about the relatively high autopsy rate is undermined if up to half the examinations performed are inadequate.

It must be emphasized that this study is concerned with fetuses >500 g birthweight and thus includes very few terminated pregnancies. Some might argue, unwisely, that in the latter instances, all that is required is confirmation of an antenatally detected malformation and therefore that histological studies are not necessary. It may be argued that the perinatal autopsy is, with the possible exception of the forensic autopsy, the most valuable and important post mortem examination performed by pathologists since it may affect the reproductive behaviour of the current generation and the quality of the next. To this end it must be remembered that negative findings are as important, if not more important, to many parents than positive diagnoses. It requires as thorough an examination to exclude disease confidently as it does to demonstrate significant pathology.

The present method of assessment of the autopsies is relatively crude and the weighting of the factors examined may be inappropriate; but it is simple and, with the exception of the clinical summary and descriptive content, it should be reproducible. It does not, however, give a complete assessment of the perinatal autopsy. No account has been taken of the experience or skill of the pathologists performing the autopsy, of the standard of histological reporting, of the facilities available to those pathologists or their workloads in other fields of histopathology. No account has been taken of how the data and observations are interpreted. Thus the recording of organ weights is of little value if they are not compared with normal values, yet gross pulmonary hypoplasia went unrecognized because normal values were not consulted. Hyaline membrane disease and bronchopneumonia were

reported in the absence of either histological or microbiological data. Implausibly, almost every major lesion of the central nervous system (excluding malformations) was classified as intraventricular haemorrhage. There are many claims on the time of general histopathologists, which may be difficult to reconcile, and while the dedicated perinatal pathologist may feel that examinations are less than adequate this is a phenomenon common to all subspecialists. But it is not the pathologist who bears the brunt of these deaths, it is the bereaved parents (Valdes-Dapena 1979; Forrest *et al.* 1982). If clinicians are to be encouraged to seek permission for autopsy on perinatal deaths then they and the parents should receive a service commensurate with the distress such deaths cause.

The recent recommendations of the Royal College of Pathologists Working Party (1990) on perinatal and paediatric pathology, if implemented, should do much to improve standards. They clearly indicate a minimum standard of investigation for the perinatal autopsy, as well as the need for ancillary investigations. The present study indicates that in many instances these minimum standards are not being attained. If the present findings apply in other areas of the country, then clinicians will be reluctant to seek permission for autopsy, and parents reluctant to give it. The inadequate or badly performed autopsy is probably worse than no autopsy at all since it may lead to a false sense of security for the parents. If pathologists are to use the autopsy to audit clinical practice then they cannot expect clinical colleagues or hospital administrators to encourage increased requests or workloads if the examinations are inadequate. The full cost of a perinatal autopsy may be £600–£1000 depending on the ancillary investigations required and the experience of the pathologist carrying out the investigation. An inadequate autopsy may cost much less but it will be a wasted investment. It is to be hoped that in the new era of users and providers in the health service, price does not outweigh quality in the closing of contracts. If it does, the future of the specialist perinatal pathologist is bleak. It is clear that audit of autopsy reports is required not only to ensure that they are of value in clinical audit, but also to ensure that the autopsies represent value for money.

Finally this study emphasises that a high autopsy rate should not be the goal of pathologists unless it goes hand in hand with a high

quality service. Parents have come to expect the highest standards from obstetricians and paediatricians. Should they not also expect the same standards from pathologists who, though they are only involved after bereavement, may contribute vital data for parental counselling?

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An analysis of factors influencing the outcome of 232 consecutive tubal microsurgery cases

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Summary. A consecutive series of 232 tubal microsurgical operations performed at the Jessop Hospital for Women, Sheffield, between 1983 and 1989, was analysed. The various contributory factors to tuboperitoneal damage were reviewed. Eighty patients (35%) conceived, resulting in 66 (29%) live births and 14 (6%) miscarriages. A further 12 (5%) had ectopic pregnancies. The overall cumulative conception rate (CCR) was 40% at the end of 50 months. Microsurgery has been most successful in the adhesiolysis group ($n=78$) with a CCR of 46% at the end of 50 months. The terminal salpingostomy group ($n=97$) had a CCR of 40% at the end of 36 months. There was a significant reduction in the live birth rate for the group with hydrosalpinx >20 mm in diameter compared with the group with <20 mm ($P=0.05$). The proximal anastomosis group ($n=27$) had a CCR of 33%. No pregnancy was reported following reconstructive surgery for multiple occlusion sites. Overall, the extent of pelvic adhesions had a significant influence on the outcome ($P=0.02$). The likelihood of conception was significantly influenced by the duration of infertility ($P=0.02$) but not affected by the aetiology of tuboperitoneal damage, parity or age of the patient. In our hands, tubo-microsurgery is more cost-effective than in-vitro-fertilization as a primary treatment of infertility due to tubal diseases.

Tubal infertility resulting from various causes of tubal damage remains a major problem. Tuboperitoneal pathology accounts for approximately 20% to 35% of all infertility and represents over 50% of the causes of infertility in women (Behrman & Kistner 1975; Fergusson 1982; Hull *et al.* 1985). Endosalpingeal destruction, oviduct occlusion, peritubal and periovarian adhesions are the factors that disturb the

physiological functions of the oviduct and which result in involuntary infertility.

The results of reconstructive surgery using conventional techniques have yielded rather poor results (Kistner & Patton 1975; Gomel 1978; Watson *et al.* 1990). In a recent study, Watson *et al.* (1990) reported a low rate of pregnancy following tubal surgery in two 'non-specialist' hospitals: the overall delivery rate was 9/82 (11%), with the delivery rate for salpingostomy 2/40 (5%). Based on these findings, Watson *et al.* (1990) and Lilford & Watson (1990) suggested that in-vitro fertilization (IVF), but not tubal surgery, should be used as the first line treatment for infertile women with tubal disease.

While the use of microsurgical techniques has produced more satisfactory results (Gomel &

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Swolin, 1980, Winston, 1980; Decherney & Kase, 1981), it has been argued that this is not so much because of special training and expertise, but a consequence of selective reporting and poor follow-up rates (Watson *et al* 1990).

With these controversies in mind, we have assessed the outcome of a consecutive, unselected series of 232 women who had tubal microsurgery at the Jessop Hospital for Women, Sheffield. Life table analysis was used to make allowance for different durations of follow-up, with a view to re-appraising the value of tubal surgery, taking into special consideration the recent development of IVF as an alternative treatment for tubal disease.

Subjects and methods

We reviewed the medical records of 232 women who underwent pelvic microsurgical procedures for infertility, resulting from various types of tubal diseases, in the University Department of the Jessop Hospital for Women from January 1983 to May 1989 inclusive. These women were followed until March 1990.

Preoperatively all the women had a complete infertility investigation. This involved a history and physical examination, assessment of ovulatory function by basal body temperature and mid-luteal phase plasma progesterone, hysterosalpingography, and diagnostic laparoscopy. Their partners underwent a general and andrological examination and had a comprehensive semen analysis, including in vitro testing of sperm penetration of bovine mucus.

No woman was excluded from operation on the basis of severity of pelvic adhesions, multiple sites of tubal occlusion, duration of infertility, or associated infertility factors.

The microsurgical procedures were performed with the use of a Wild operating microscope (Leitz Instruments Ltd, Luton, UK). The reconstructive microsurgical techniques employed were similar to those described by Swolin (1975) and Gomel (1977, 1980a). The techniques included atraumatic tissue handling, fine suture material (4-0 to 8-0 polyglactin (Vicryl; Ethicon) and polypropylene, constant irrigation of the tissue with a physiological solution that contained heparin (1000 u/l), blended unipolar cautery for haemostasis and lysis of adhesions. Peritoneal defects were covered by approximating with 4-0 polypropylene sutures or with free omental grafts. As recommended by

Swolin (1967), 750 mg of hydrocortisone acetate in 50 ml of 10% Intralipid (fractionated soya bean oil, Kabivitrum, Bourne End, Herts., England) was instilled into the peritoneal cavity before closure, with a view to reducing adhesion formation.

To permit comparison of our results with those of other investigators, surgical procedures were classified into categories defined by the International Federation of Fertility and Sterility (Gomel 1980b).

Postoperatively, prophylactic antibiotics were given for 5 days. Parenteral corticosteroids before or after surgery were not used and post-operative hydroperturbation was not performed.

The follow-up data were obtained from the hospital records, contact with the women by letter or telephone, or contact with their general practitioners.

Selection criteria for tubal surgery

In our series, the only absolute contraindication for microsurgery was pelvic tuberculosis. Women were considered suitable for microsurgery even if other additional infertility factors were present, such as ovulatory dysfunction or subfertility of the male partner, on the grounds that these factors could be treated post-operatively. In addition, we did not impose an age limit as some other investigators have done (Gomel 1978). Similarly, previous attempts at tubal surgery did not result in exclusion. The operations were performed by a number of different surgeons and, as such, represent a series of unselected cases of tubal surgery performed in a teaching hospital with a special interest in infertility management.

Statistical analysis was performed by using the Statistical Package for Social Sciences (SPSS-X), available within the IBM 3083 at the University of Sheffield. Statistical analysis was carried out by contingency table analysis as well as life table analysis (Cramer *et al* 1979).

Results

The study population consisted of women between the ages of 20 and 42 years (mean 30.4 years). Of the 232 women, 125 (54%) had primary infertility whilst 107 (46%) had secondary infertility. The mean duration of infertility was 5.2 years and ranged between 1 and 20 years. A total of 217 (94%) women were fol-

lowed up successfully. The mean duration of follow-up was 2.8 years (range 10 months to 6 years). The possible aetiological factors of tuboperitoneal damage are summarized in Table 1.

Overall success rate

The crude pregnancy outcome was determined for each category of microsurgical procedures. Women lost to follow-up were considered to be not pregnant. The cumulative conception rates for each group are shown in Fig. 1 (a-d). Overall, a rate of 25% was observed at 12 months and a rate of 40% at the end of 50 months.

Success rate by the type of surgery

Adhesiolysis. Seventy-eight women were found to have pelvic adhesions as a sole cause of their infertility with bilateral tubal patency on hysterosalpingography and laparoscopy. The results are shown in Table 2. Figure 1b shows the cumulative conception rate after adhesiolysis. The rate for the adhesiolysis group at the end of 50 months appears to be the highest among the various subgroups.

Salpingostomy. Ninety-seven of 232 women were treated with terminal salpingostomy for unilateral or bilateral distal tubal occlusion of varying pathology. The intrauterine conception rate was essentially the same after bilateral salpingostomy (35%) as after unilateral salpingostomy (32%) performed because of an absent, normal or irreparable contralateral oviduct.

The cumulative conception rate for the salpingostomy group (Fig. 1c) shows that 28% of the women achieved a pregnancy at the end of 12

months. The probability of conception during the second year rose steadily and was 40% at the end of 36 months; hence the majority of conceptions occurred within 18 months after the operation

When pregnancy outcome was examined according to the size of the hydrosalpinx, a significantly smaller ($P=0.05$) live birth rate was found for the group with a hydrosalpinx of >20 mm ($2/24 = 14\%$) compared with those with a hydrosalpinx of <20 mm ($19/70 = 27\%$) and those with no hydrosalpinx ($6/13 = 46\%$). This grouping was made according to the size of the lesser hydrosalpinx, if both tubes were present, or that of the hydrosalpinx on the remaining tube if only one was present. On the other hand, the difference in the ectopic pregnancy rates between the group with a large hydrosalpinx ($1/14 = 7\%$) and the group with a small hydrosalpinx ($6/70 = 8\%$) was not significant.

Tubocornual anastomosis. Tubocornual anastomosis was performed in 33 women, of whom six had combined proximal and distal occlusions. No pregnancy was recorded after surgical correction for proximal and distal tubal occlusion on the same side. The cumulative conception rate for tubocornual anastomosis appears to be lowest among the three major subgroups.

Tubotubal anastomosis. Mid-segment tubotubal anastomosis for pathological conditions was performed in five women. Of these, unilateral congenital segmental non-canalization of the oviduct was encountered in one woman. In two a condition of arrested tubal gestation was found at laparotomy. In another two women, ampullo-isthmic anastomosis was performed because

Table 1. The occurrence of possible aetiological factors of tuboperitoneal damage among 232 patients who underwent tubal surgery between 1983 and 1989

1	Presumed pelvic inflammatory diseases (PID)	75 (32%)
	pregnancy related	24
	unrelated to pregnancy	51
2.	Previous abdominal/pelvic surgery*	62 (27%)
	appendicectomy	39
	tubal surgery	17
	salpingectomy or salpingo-oophorectomy for tubo-ovarian masses	17
	ectopic pregnancies	21
	others	10
3.	Endometriosis	40 (17%)
4	No apparent aetiological factors	55 (24%)

*Some patients had more than one of the above in their past surgical history.

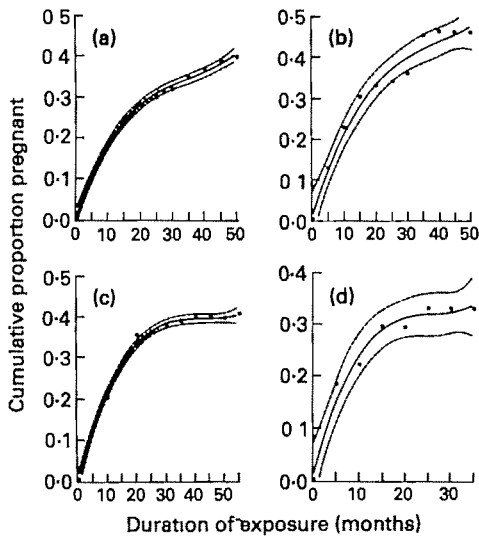


Fig. 1. (a)—Cumulative conception rate (CCR) for all microsurgical procedures (fitted mean with 95% confidence limits); (b)—CCR following adhesiolysis; (c)—CCR following salpingostomy, (d)—CCR for tubocornual anastomosis group.

there had been previous mid-segmental excision for tubal gestation. Among this group, only one live birth occurred after reconstruction of a congenital segmental non-canalization of the oviduct and one woman had a further ectopic pregnancy.

Tubouterine implantation. Bilateral tubouterine implantation was done in nine women because of pathological interstitial occlusion. In this group, we achieved only two intrauterine pregnancies, resulting in one live birth and one mis-

carriage. The numbers in these and other remaining categories (Table 2) are too small for analysis by cumulative conception rates.

Analysis of other factors influencing the success rate

Age. This did not have any significant effect on pregnancy rate in the current series. The conception rates in various age groups were: 21–25 years, 27%; 26–30 years, 38%; 31–35 years, 32%; 36 and above 36% and these were not statistically significantly different from each other.

Parity. In the current series, the likelihood of conception following tubal microsurgery was not influenced by parity, as the proportion of nulliparous women who conceived (32%) was again not statistically significantly different from that of parous women (37%).

Duration of infertility. The duration of preoperative infertility varied from 2 to 20 years (mean 5.2 years). The duration of infertility had a significant influence on the outcome of surgery ($P=0.01$). Women who had been infertile for a longer duration were less likely to conceive following tubal surgery (Table 3).

Severity of adhesions. Despite the limitations of the retrospective study of the operative reports, a reasonable estimation of the extent of the adhesions was possible and was expressed as mild, moderate or severe. When the severity of pelvic adhesions was analysed with respect to pregnancy outcome, lower conception and live birth rates were found with increasing severity of

Table 2. Pregnancy outcome of all microsurgical operations in 232 women

Microsurgical procedure	Total no. of women	Intrauterine pregnancy	Live birth	Miscarriage	Ectopic pregnancy
		<i>n</i> (%)	<i>n</i> (%)	<i>n</i> (%)	<i>n</i> (%)
Adhesiolysis (alone)	78	32 (41)	29 (37)	3 (4)	4 (5)
Salpingostomy (alone)	97	33 (34)	28 (29)	5 (5)	6 (6)
Tubocornual anastomosis	27	9 (33)	6 (22)	3 (11)	2 (8)
Tubocornual anastomosis with simultaneous salpingostomy	6	—	—	—	—
Tubotubal anastomosis	5	1 (20)	1 (20)	—	—
Tubouterine implantation	9	2 (22)	1 (11)	1 (11)	—
Salpingostomy with other procedures	10	3 (30)	1 (10)	2 (20)	—
Total no.	232	80 (35)	66 (29)	14 (6)	12 (5)

Table 3. The proportion of women who conceived after microsurgery by duration of infertility

Duration of infertility (years)	Total no. of women (%)	Intrauterine* pregnancy	Live birth*	Miscarriage	Ectopic pregnancy
		n (%)	n (%)	n (%)	n (%)
2-5	147 (63)	62 (42)	52 (36)	10 (7)	6 (4)
6-9	61 (26)	14 (23)	11 (18)	3 (5)	5 (8)
10-13	18 (8)	3 (17)	2 (11)	1 (5)	1 (5)
≥14	6 (3)	1 (17)	1 (17)	—	—

The results in each of the four duration-of-infertility groups are compared to the others by contingency table analysis.

* $P=0.01$.

pelvic adhesions: no adhesions, 7/10 (70%); mild adhesions, 24/57 (42%); moderate adhesions, 34/104 (36%); dense adhesions, 15/61 (25%) ($P=0.025$, contingency table analysis).

Endometriosis. Forty patients undergoing surgery had clear evidence of endometriosis. The American Fertility Society (1979) classification was followed to assess the extent of endometriosis. A significant association between the extent of endometriosis and pregnancy rates was established: mild, 9/16 (56%); moderate, 5/10 (50%); severe, 2/14 (14%) ($P=0.025$, contingency table analysis). Surprisingly only one ecto-

pic pregnancy was reported in the group where endometriosis was found to be an aetiological factor for tuboperitoneal disease.

Aetiological factors. There was no difference in the pregnancy rates according to the various aetiological factors of tuboperitoneal damage ($P=0.34$).

Associated infertility factors. In 75 of the 232 women (32%) there were one or more additional infertility factors. Subfertility of the male partner impaired the chances of conception in another 12%. Four couples accepted insemination with donor semen as the only possibility of pregnancy. One of these conceived after 11 treatment cycles and had a term pregnancy. Three were treated with bromocriptine for hyperprolactinaemia, 34 received clomiphene citrate and seven gonadotrophins for anovulation. Fourteen women failed to conceive after ovulation induction. One woman had premature ovarian failure at the age of 35 years. The cumulative conception rates in these women with associated infertility disorders were 15% at the end of 20 months and 22% at the end of 50 months. In women with no other identifiable factors, the cumulative conception rate was 40% at the end of 50 months (Fig. 2).

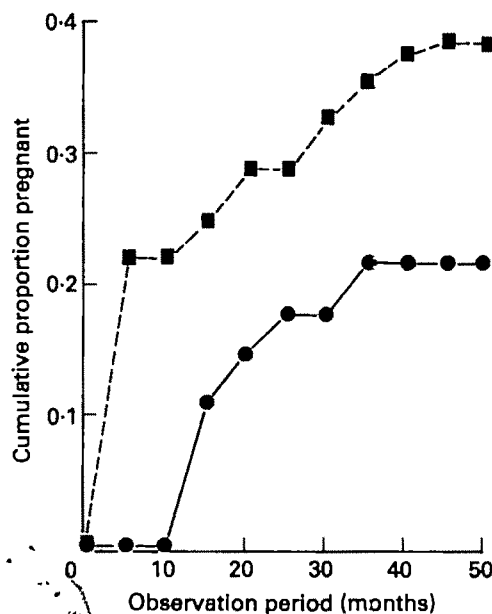


Fig. 2. Cumulative conception rate (CCF) for women with no other infertility factors (---) and those with associated infertility factors (—).

Discussion

Assessment of the results of tubal microsurgery is difficult as pointed out by Cooke *et al.* (1981), because components of microsurgical technique are imperceptibly being incorporated into macrosurgery. Comparisons of reported conception rates after microsurgical procedures are also difficult because numerous factors may affect the success rates. Some of these factors include a

Table 4. The aetiological factors of tubal disease and their influence on outcome of microsurgery

Aetiology	Total no. of women (%)	Intrauterine* pregnancy	Live birth*	Miscarriage	Ectopic pregnancy
		n (%)	n (%)	n (%)	n (%)
Idiopathic	55 (24)	24 (44)	20 (36)	4 (7)	3 (5)
Pelvic inflammatory disease	75 (32)	18 (24)	14 (19)	4 (5)	4 (5)
Previous pelvic/abdominal surgery	62 (27)	22 (37)	18 (32)	4 (6)	4 (6)
Endometriosis	40 (17)	16 (40)	14 (35)	2 (2.5)	1 (1.5)

The results in each of the four aetiology groups are compared to the others by contingency table analysis. * $P=0.01$

degree of pre-existing tubal damage, surgical technique, patients' age and selection, extent of follow-up and methods of pregnancy reporting. However, Jacobs *et al.* (1988) strongly recommended that each microsurgeon and institution must establish their own conception rates in order to be able to inform patients who are considering microsurgical reconstruction.

Adhesiolysis

In this series, after adhesiolysis using microsurgical techniques, 42% of the women conceived and the cumulative conception rate was 46% at the end of 50 months. The cumulative rate may be helpful when advising women about their prognosis for a conception before resorting to in vitro fertilization and embryo transfer (IVF-ET). By using life table analysis pregnancy results can be corrected for variability of follow-up intervals. It gives a better measure of the success of the therapy than the observed unadjusted pregnancy rate (Cooke *et al.* 1981), since the latter does not take into consideration women lost to follow-up early in the study. Some series have shown higher success rates after adhesiolysis (Bronson & Wallach 1977; Diamond 1979). It is difficult to compare the different series of adhesiolysis in view of the important differences that exist in the extent and nature of periadnexal and pelvic adhesions. Adhesiolysis is sometimes more difficult than tubal repair itself. Division of adhesions between tubes, ovaries and bowel or omentum takes much time and experience. Great care should be taken to avoid damage to the vessels that supply the fimbriae. Every effort should be directed to preventing postoperative adhesions (Diamond 1979). The influence of local corticosteroids in reducing

adhesion formations has been demonstrated by Swolin (1967).

Salpingostomy

In women who had microsurgical terminal salpingostomy for distal occlusion, the chances of success are a little more promising. The overall conception rate in the present series following salpingostomy agrees with many other series (Gomel & Swolin 1980; Donnez & Casanas-Roux 1986a). In this group 34% achieved one or more intrauterine pregnancies and 29% had one or more live births. Six women (6%) had ectopic pregnancies. This series includes six women who had previously had salpingostomies performed elsewhere by gross conventional methods. Swolin (1975) achieved a term pregnancy rate of 27% in 33 patients, and in a series of 89 women treated with pure salpingostomy, Gomel & Swolin (1980) achieved a term pregnancy rate of 33.7% and ectopic pregnancy rate of 9%.

Some of the prognostic factors that have been shown to be associated with pregnancy outcome after salpingostomy include the nature and extent of tubovarian adhesions (Boer-Meisel *et al.* 1986; Hulka 1982), tubal damage (Vasquez *et al.* 1982), the rugal pattern of the tubes as seen on hysterosalpingography (Young *et al.* 1970), the thickness of the tubal wall and the size of the hydrosalpinx (Shirodkar 1966). In the current series, pregnancy outcome was significantly related to the size of the hydrosalpinx. Patients with tubes of normal diameter had a higher pregnancy rate (54%) compared with those having moderate (30%) and severe dilatation of the tube (21%).

Tubocornual anastomosis

With the use of microsurgical techniques tubocornual anastomosis has largely replaced tubouterine implantation for proximal tubal damage. Winston (1980), Gomel (1983), Gillett & Herbison (1989), and Patton *et al.* (1987a) reported term pregnancy rates ranging from 37% to 60% following tubocornual anastomosis for proximal tubal blockage. The chance for a term pregnancy after tubocornual anastomosis in this series was only 22%.

Some of the prognostic factors for tubocornual anastomosis seem to be isthmic residual length, preservation of the intramural segment and excision of all pathological tissue (Winston 1980; Donnez & Casanas-Roux 1986b). However, Winston (1980) has emphasized the importance of careful anatomical reconstruction with good magnification and accurate placement of sutures. Tubocornual anastomosis may be technically very difficult and the learning curve is longer.

Combined procedure

Combined proximal and distal tubal occlusion was encountered in six women and no pregnancy was reported after combined procedures. Pregnancy rates have been poor in patients with multiple sites of occlusion (Patton *et al.* 1987b). The diagnosis of the combined proximal and distal occlusion, with its grim prognosis, may not be established until the time of the microsurgical procedure. Patients should be advised of these possibilities and should consider IVF-ET whenever preoperative assessment raises the suspicion of combined proximal and distal occlusion in the oviduct.

Endometriosis

In our series endometriosis of varying degree was associated with 17%. Although many investigators have reported that expectant management of mild to moderate endometriosis after diagnostic laparoscopy is fairly successful, with pregnancy rates of approximately 50% (Hull *et al.* 1987, Olive & Haney 1986; or Thomas & Cooke 1987), conservative surgery has been thought to offer better prospects than medical treatment (Hammond *et al.* 1976). The pregnancy rates remain low in patients with severe endometriosis, despite vigorous medical and surgical treatment.

Age

Although age is generally recognized to have a negative effect on fertility potential of women in large population studies, due to increased ovulatory disturbances, it did not have nearly as great an effect on pregnancy rate in the current series. Gomel (1983) pointed out that in all societies age-specific fertility decreases appreciably after the age of 35 and more notably after 40. An influence of age on success rate is likely. Provided that a woman is capable of making a mature informed judgement after full discussion, we prefer to permit an individual decision to be made by these particular women. Of course the imposition of an age limit for microsurgical candidates might also result in better statistics.

Duration of infertility

In this series, the duration of infertility had a significant influence ($P=0.024$) on the outcome of reconstructive surgery which is in contrast with the findings of Bronson & Wallach (1977).

Co-existing infertility factors

In our study, the presence of co-existing infertility factors appeared to limit the success of reconstructive tubal surgery; 32% of patients in this series were found to have associated infertility factors.

There were fewer pregnancies as measured by the cumulative conception rate in women with associated infertility factors, as compared with the group suffering from a tubal factor alone (Fig. 2). In each of these, the difference, while clinically suggestive, was not statistically significant. Thus, ovulation disorders and subfertility of the male partner may influence the overall results and careful preoperative assessment and counselling are mandatory.

Microsurgical training and equipment

The extent to which specialized training, the availability of various microsurgical instruments including the operating microscope, the application of microsurgical skills and experience, may influence the outcome of tubal surgery is difficult to quantify. However, many believe that these are of considerable importance. The low success rate reported by Watson *et al.* (1990) from two non-specialist hospitals supports the argument that specialized training, experience

and equipment in microsurgery has a major impact on the outcome of tubal surgery. In this study, the results are based on a consecutive series of women operated upon by a number of different surgeons (a number in training), with varying degrees of experience. However, all observed the same microsurgical principles and employed similar instruments. Thus, the results reported in our study represent not what can be achieved by a special individual, but by a team of gynaecologists practising microsurgery. In this respect, the results are realistic, and likely to be reproducible in other units practising tubal microsurgery.

In view of the poor results in those who had repeat tubal surgery, Taylor & Leader (1984) suggested that the first attempt at repair is the one most likely to yield success, and the patients deserve the services of a trained tubal surgeon in the first instance

Tubal surgery compared with IVF

The overall delivery rate of 29% in this consecutive series of tubal microsurgery seems more encouraging than the 11% recently quoted by Watson *et al.* (1990). Lalford & Watson (1990), basing their estimate on an average cost for tubal surgery of £1000 and a 5% success rate after salpingostomy, calculated that the cost for each baby born as a result of tubal surgery (salpingostomy) would be £20 000. However, using their financial estimates and our results, i.e., successful pregnancy rate following salpingostomy of 28%, the corresponding cost for each baby born is only £3500. The same figure is true for all types of tubal microsurgery considered together in our series. The cost of successful pregnancy per tubal microsurgery is significantly lower than the average national figure quoted for viable pregnancy achieved by IVF (£11 000, Page 1989).

It could of course be argued that the figure quoted above for IVF is an average, and that in selected centres that have achieved outstanding success rates for IVF, the cost may be less. However, it could also be argued that the success rate of tubal microsurgery quoted above is also an average, based on a consecutive series of women. The results shown in Tables 2-4 suggest that they could be improved by as much as 50%, if only those with good prognostic factors, such as those with no or minimal hydrosalpinges or adhesions, or shorter duration of infertility, are selected for surgery. The results are likely to be

further improved if a personal series of the most experienced surgeon, rather than that of the whole unit (including a number of surgeons in training), is selected for analysis.

On the other hand, consideration of the various factors affecting the outcome of tubal microsurgery allows the identification of those who are more likely to have a poor prognosis following microsurgery, such as those with multiple blocks and large hydrosalpinges. Perhaps it is in this category of patients that IVF may be considered as an alternative primary treatment. Apart from those with simultaneous, proximal and distal blocks, the successful pregnancy rate following tubal microsurgery in various categories is not less than 10%. The cost-effectiveness of tubal surgery with a success rate of 10% is still comparable to that of IVF. The live birth rate per treatment cycle for even large centres in 1988 was 10.1% (ILA 1990).

Thus, there is little doubt from our data that tubal microsurgery overall is more cost-effective than IVF. For this and other reasons discussed by Winston & Margara (1987), tubal microsurgery is likely to continue to play an important role in the treatment of infertility due to tubal diseases.

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Microsurgical salpingostomy is not an obsolete procedure

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Abstract

Objective—A review of the results of microsurgery for bilateral distal tubal blockage.

Design—A retrospective review

Setting—Hammersmith Hospital London and local private hospitals.

Subjects—388 patients with bilateral ampullary occlusion treated between 1971 and 1988 by microsurgery.

Interventions—Full investigation for other causes of infertility followed by abdominal microsurgical salpingostomy. Repeated meticulous follow-up was essential with check laparoscopy one year after surgery.

Main outcome measure—Successful pregnancy in relation to tubal damage.

Results—In 65 women microsurgery followed tubal reocclusion after failed conventionally performed salpingostomy. 74 women (23%) had one term pregnancy after primary salpingostomy and 12 women (18%) after repeat salpingostomy. Over half the women having a term pregnancy subsequently had a second infant. The tubal damage was classified in four stages according to the degree of mucosal damage and tubal fibrosis, the presence of isthmic disease and the quality of tubal and ovarian adhesions. Approximately one quarter of patients had stage I disease and amongst these 39% had babies after primary salpingostomy and 25% after repeat salpingostomy.

Conclusion—Microsurgical salpingostomy is a specialized procedure. Proper selection of patients, competent microsurgical technique and adequate follow-up appear crucial to success. In selected patients treatment by salpingostomy gives better results than multiple cycles of in vitro fertilization.

Increasing use of in vitro fertilization (IVF) for women with tubal inflammatory disease had led to decreasing focus on the possibilities that tubal microsurgery offers patients. Lilford & Watson (1990) even believe that IVF has now replaced microsurgery when the distal portion of the fallopian tube is blocked. Treatment of hydrosal-

pinges undoubtedly gives the least good results of all common fertility operations but in this study we report the results of microsurgery for bilateral distal tubal blockage and the results indicate that salpingostomy is far from being an obsolete operation. Moreover, salpingostomy is the only treatment which offers potential restoration of natural fertility.

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Subjects and methods

Between 1971 and 1988 a total of 388 abdominal operations for salpingostomy were done by surgeons from Hammersmith Hospital; some of these operations were done at local private hospitals. The age range of the patients was 19–44

years (mean 31.5 years); 27 patients were 42 or older. All the couples were carefully investigated before surgery for other causes of infertility, semen analysis, luteal phase plasma progesterone assays, and a postcoital test were performed. A second cause of infertility was not regarded as a contraindication to surgical treatment. Nearly all patients had hysterosalpingography (HSG) before surgery and, before surgery was scheduled, laparoscopy was undertaken by one of the authors or his senior registrar. In most patients treated after 1977, several laparoscopic photographs were also taken for thorough documentation. Because combining laparoscopy with immediate open surgery might be clinically detrimental and psychologically undesirable (i.e., no prior discussion of prognosis or management with the couple), laparoscopy and microsurgery were separated by a minimum of one week.

In this series, only patients who had open surgery are included; results of laparoscopic salpingostomy, of which we have some experience, will be published separately. Salpingostomy is defined in this study as an operation to open the terminal portion of a completely closed fallopian tube; all those who had salpingolysis or fimbrioplasty where one or both tubes were partially patent are excluded. In some patients only one tube was operated on, for example after previous salpingectomy or where we considered that a tube was so badly damaged as to be inoperable. Patients with obvious severe cornual damage or bipolar blockage were also excluded from this study.

Microsurgery

Full microsurgical methods were used. In a few early procedures, magnifying loupes were used, but in 349 patients (90%) a Zeiss operating microscope was used at magnifications between $\times 4$ to $\times 25$. We switched to the microscope because we obtained superior dissection and less tissue damage. Terminal salpingostomy was undertaken except when tube wall fibrosis was so pronounced as to make this not feasible. Micro-electrodiathermy was used routinely, except in nine procedures where a carbon dioxide laser was employed. Our technique has already been described (Winston & Margara 1986) and included precise haemostasis, isotonic irrigation, avoidance of serosal damage, peritoneal lavage and the administration of anti-

biotics, and the use of corticosteroids in many patients who also had adhesiolysis. Postoperative hydrotubation was not done, except early in the series in 34 women. Patients were discharged from hospital 4–7 days after surgery, except for five cases who had a wound infection or dehiscence and one other woman with suspected pulmonary embolism, who was discharged fit 10 days postoperatively.

Follow-up

Repeated, meticulous follow-up was considered essential. Some women, usually from overseas, could not be followed regularly, but most were examined one month after surgery and thereafter at 3-month intervals until pregnancy occurred or until discharge from our clinic or admission for IVF. Tests for ovulation and semen analysis were repeated during the sixth postoperative month. Anovulatory patients were given clomiphene and/or gonadotrophins for a minimum of 3 months and usually longer. In 23 couples severe abnormalities of semen quality led to donor insemination being offered; we have incomplete information about the number of cycles undertaken as these couples were generally referred outside Hammersmith. Check laparoscopy was offered to all patients, except those entering the IVF programme, one year after surgery. This was accompanied by closed adhesiolysis when indicated and chromoperturbation; HSG was not usually repeated. Of 272 patients having check laparoscopy within approximately one year after salpingostomy, 223 (82%) had at least one tube patent to dye.

The widespread nature of our referral practice means that some women were lost to follow-up. We have assumed that if a woman was lost to follow-up or did not answer inquiries, she had not had a successful pregnancy. Follow-up information was available on all but 47 women (12%) one year after surgery and in 58 follow-up has been maintained for over 10 years. The longest interval to successful pregnancy was 7 years. All patients operated but lost to follow-up are included in our results and reported as failures. This may introduce a slight bias in reporting and it is possible that there have actually been more livebirths than reported.

Results

In 323 patients salpingostomy was a primary pro-

Table 1. Distribution of women with pregnancies after tubal surgery*

Patient group	n	Numbers of women having a pregnancy			
		At least one term pregnancy	More than one term pregnancy	Intrauterine pregnancy	Ectopic pregnancy
Primary salpingostomy	323	74 (23%)	39	106 (33%)	32 (10%)
Repeat salpingostomy	65	12 (18%)	7	16 (25%)	6 (9%)
Total	388	86 (22%)	46	122 (31%)	38 (10%)

* Some women having a miscarriage or ectopic pregnancy also achieved a term pregnancy.

cedure, although some of them had already had a laparotomy associated with their infertility. In the remaining 65 women, the salpingostomy was a repeat procedure after previous salpingostomy by other surgeons working without a microscope had resulted in tubal reocclusion.

Overall, 86 women had at least one infant (Table 1); there were two sets of twins, one set identical. Over half the women having one live-birth subsequently had a second infant and 19 had three or more births. One patient, following repeat salpingostomy on her sole tube (removal of the other having resulted from an ectopic), had five separate term pregnancies.

Table 2. Staging of tubal disease in hydrosalpinges

Stage I	Thin-walled hydrosalpinx with little or no fibrosis Mucosa thrown into folds with no flattened areas Adhesions (if present) flimsy and limited to the ampulla and ovary only. Ovary present and mainly free.
Stage II	Thick-walled hydrosalpinx with good mucosa. Mucosa flattened with attenuated or few folds but thin-walled tube. Mucosal folds markedly adherent in lumen Fibrous thick adhesions involving tube and/or ovary
Stage III	Combination of thick walled hydrosalpinx with marked mucosal damage or thick fibrous adhesions. Clean hydrosalpinx with thin wall but with nodularity of patent isthmus Ovary incarcerated against pelvic side wall or absent on that side.
Stage IV	Tubo-ovarian mass or fibrous, adherent hydrosalpinx with incarcerated ovary and/or isthmic damage.

Assessment of tubal pathology

In 1979 it became clear to the authors that a factor in the outcome of tubal surgery was the degree of tubal damage and the stage of disease. We are indebted to Dr Margt Boer-Meisl of Amsterdam who drew our attention to her own method of classification of tubal damage, which we have modified (Table 2). In a retrospective analysis, when adequate operative records were available and/or good quality laparoscopic photographs and HSG pictures, we scored the degree of tubal pathology into four categories (Table 3). This was possible with reasonable accuracy in 230 of those who had a first salpingostomy and in 61 of those who had a repeat salpingostomy.

Histology from one or both tubes was available for 74 of the women and most showed non-specific inflammatory changes or chronic follicular salpingitis. There were five examples of histologically confirmed tuberculosis; remarkably two of these women gave birth after microsurgery. Tubal epithelial microbiopsies (Brosens & Vasquez 1976) were taken from 48 women and mucosal ciliated cell counts were made within a few weeks of salpingostomy before the clinical outcome was known. Ciliated cells were counted using scanning electron micrographs and semi-thin sections by methods described previously (Vasquez *et al.* 1982). These patients were then followed prospectively and the outcome related to ciliated cell counts (Fig. 1).

Discussion

In their recent commentary in this journal, Lilford & Watson (1990) state that salpingostomy is obsolete. The present substantial series does not support this contention. Salpingostomy carries very poor results with badly damaged tubes and

Table 3. Pregnancy outcome related to stage of disease in the better or only tube

Patient group	n	Term pregnancy	Ectopic pregnancy
Primary salpingostomy (n = 230)			
Stage I	56	22 (39%)	8
Stage II	99	20 (20%)	12
Stage III	58	5 (9%)	2
Stage IV	17	1 (6%)	0
Repeat salpingostomy (n = 61)			
Stage I	44	11 (25%)	4
Stage II	10	4 (40%)	2
Stage III	6	(0%)	0
Stage IV	1	(0%)	0

only 6 of 82 patients (7.3%) had a successful outcome where the stage of disease was worse than stage II. However, 57 of 209 patients with lesser disease (27%, Table 3) had at least one live birth. These figures underline the importance of proper preoperative management and it is strange that surgeons undertaking this specialized branch of surgery do not recognize that the degree of pathology is a critical factor in results. Gynaecological oncologists have acknowledged this principle for years, and Wertheim hysterectomy is not to be abandoned simply because it is inappropriate for stages III or IV carcinoma of the cervix.

Preoperative assessment requires expertise,

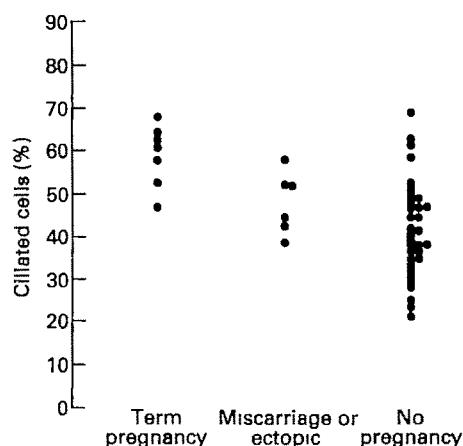


Fig. 1. The percentage of ciliated surface area from tubal microbiopsies taken at 48 primary operations. More patients with successful pregnancy had good ciliated epithelium. Term pregnancy: median ciliated surface 59.2% (SD 7.4), failed pregnancy: median ciliated surface 49% (SD 7.4); not pregnant: median ciliated surface 39% (SD 11.8). These differences were not statistically significant.

both in detailed laparoscopy and in the accurate reading of clearly taken salpingograms. Although it is difficult to assess mucosal pathology before the tube is examined at surgery, tubal fibrosis or concomitant cornual damage can be pinpointed with accuracy on a good radiograph and the quality of adhesions and the state of the ovarian surface are capable of precise laparoscopic assessment. Regrettably, HSG has largely been relegated by most clinicians and few surgeons performing laparoscopy record precise information about tubal and ovarian pathology; regular documentation by photography—a cheap, effective record—is almost unknown in Britain.

A disappointing feature is that most patients with hydrosalpinges have relatively badly damaged tubes. Only 56 out of 230 women undergoing primary salpingostomy had damage classified as stage I; this proportion (24%) is probably representative of hydrosalpinges in

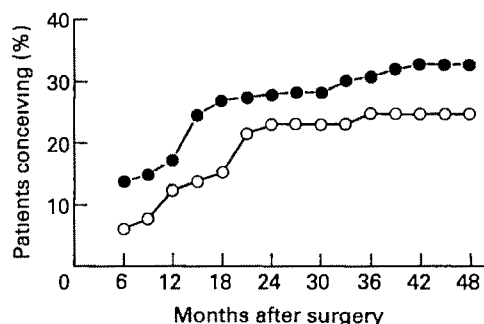


Fig. 2. Cumulative conception expressed as percentage of patients conceiving at 3-month intervals. There was a slight increase in conception rate immediately after completion of one year's follow up which is not statistically significant. —●—, Primary salpingostomy; —○— Repeat salpingostomy

general as we offered tubal surgery to most patients who had not had a previous salpingostomy. We were much more selective in offering surgery if this had already failed and the 65 women who had repeated salpingostomy were carefully picked. Only 100 of all patients had disease which could be classified as stage I, but 33 of these had term pregnancies. In such women, particularly those that are relatively young, tubal microsurgery should be the treatment of choice. Opting for surgery does not preclude subsequent IVF and, in our practice, we increasingly offer both treatments in tandem.

Of the 106 women in the primary salpingostomy group who had at least one intrauterine pregnancy, 55 occurred within one year of the procedure, of the 16 intrauterine conceptions in the repeat salpingostomy group, six occurred within one year of the procedure.

Conception seldom happened immediately after surgery (Fig. 2). Conception was more rapid in those patients with stage I disease in both groups. Conception rate improved slightly after one year. This effect has been attributed (Gomel 1978) to epithelial regeneration, though there are no hard data. Another possible explanation for this effect is that check laparoscopy was usually performed one year after microsurgery and a number of pregnancies happened within two to three months of laparoscopy—perhaps the result of washing through the tubes by hydrotubation at the time of laparoscopic examination. The delayed return to fertility is a definite disadvantage when compared to IVF but the reassurance that a woman feels at being able to conceive naturally after completed treatment was a major benefit to many patients. Moreover, more than half the patients who gave birth had more than one child without extra risk of multiple pregnancy.

It is our impression that open salpingostomy may be better than that done laparoscopically. Open microsurgery gives better anatomical results; at check laparoscopy one year after surgery, complete bilateral reocclusion was observed in only 12% of women after 181 microsurgical procedures compared with 37% after 37 laparoscopic operations (14 cases). Tubes with more pronounced damage were more likely to reocclude and, in general, most of our laparoscopic salpingostomies have been done when there was minimal damage only.

Repeat salpingostomy is a procedure which has been mostly abandoned by surgeons. Our

report includes the biggest published series of repeat salpingostomies and it demonstrates that even repeat salpingostomy is helpful in certain patients with limited damage. All the repeat operations were after failed 'gross' surgery. These results suggest that the degree of tubal pathology and the use of microsurgical technique influence success.

Tubal surgery, including salpingostomy, should not be halted in favour of IVF. The results of salpingostomy in our hands and in the hands of surgeons trained by us do not support this view. The term pregnancy rate overall was better than that achieved by nearly all IVF programmes, and in patients with stage I disease was better than four times the national average for a single IVF treatment cycle (9.1%, ILA report 1990). It is ludicrous to suggest that repeated cycles of IVF compare favourably with microsurgery in this latter group of women. The cost of four cycles of IVF will be a minimum of £4000 and even more treatments would be required for couples to have a completed family. Moreover, IVF programmes cannot cope with the demand. The ILA report that only some 7000 women received one or two treatments last year; most National Health Service programmes have very long IVF waiting lists. It is unrealistic to suppose that IVF can currently meet the need of most women with the common problem of tubal blockage.

The authors confess to being unrepentant tubal surgeons. The results we report are not isolated; other practitioners of microsurgery, all overseas, have published comparable results in smaller series (Swolin 1975; Gomel 1978; Salat-Baroux *et al.* 1979; DeCherney & Kase 1981; Larsson 1982; Wallach *et al.* 1983; Lauritsen *et al.* 1983; Sadoul *et al.* 1984; Donnez & Casanaroux 1986; Kitchin *et al.* 1986). We jointly run one of the largest and more successful of the IVF programmes in Britain but are convinced that, with experienced selection of cases, tubal microsurgery is an effective and important treatment. Salpingostomy still has a place, particularly in young women and those with limited tubal damage. It remains the treatment of choice for some, but must be done using good microsurgical technique and with regular follow up. It is not acceptable to offer these unfortunate women crude surgery which has little or no chance of success and which simply delays effective management. Microsurgical salpingostomy is a specialized procedure and it would be preferable to ensure

better training in the selection and management of these patients rather than to turn to the expensive and often inappropriate option of IVF. Regrettably, the sub-specialty training programmes of the Royal College of Obstetricians and Gynaecologists have paid insufficient attention to the value of microsurgery in the United Kingdom and this deficiency needs urgent redress.

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Is GIFT (gamete intrafallopian transfer) the best treatment for unexplained infertility?

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Abstract

Objective—To compare the cumulative pregnancy rates after gamete intrafallopian transfer (GIFT) with the cumulative spontaneous pregnancy rates in couples with unexplained infertility.

Design—A contemporaneous study in a single group of patients.

Setting—Northern Regional Fertility Centre.

Subjects—76 couples with unexplained infertility of more than 3 years duration

Interventions—Successful pregnancies were recorded during at least 3 months before GIFT and up to 21 months after a maximum of three cycles of GIFT treatment

Main outcome measures—Pregnancy resulting in a live birth.

Results—Average monthly fecundability without treatment was 0.021 and after GIFT was 0.14 ($P < 0.001$). This was reflected as a cumulative pregnancy rate of 52% after three cycles of GIFT and 30% after 24 months without treatment.

Conclusions—The chance of having a baby after one cycle of GIFT is significantly greater than the chance in a spontaneous cycle. However, considering the cumulative pregnancy rates, we suggest that if GIFT is to be a realistic treatment option, it should be offered for more than one cycle.

Gamete intrafallopian transfer (GIFT) (Asch *et al.* 1985) is increasingly recommended as the treatment of choice for unexplained infertility. In 1987, 2288 couples were treated and 50 centres in the UK offered GIFT (Fourth Report of the Voluntary Licensing Authority 1989). Recent trends would suggest that these numbers

will continue to increase. The overall pregnancy rate per cycle is 19% in the UK (Fourth Report of the Voluntary Licensing Authority 1989).

Couples with unexplained infertility still have a chance of spontaneous conception (Collins & Rowe 1989, Templeton & Penney 1982; Lenton *et al.* 1977). No study has yet been reported which demonstrates that the success rate for GIFT is greater than the spontaneous pregnancy rate within the same group of patients.

We therefore present a study of contemporaneous spontaneous pregnancy rates with pregnancy rates following GIFT in couples with unexplained infertility. The number of cycles of GIFT offered was limited by financial considerations. Spontaneous conception was monitored for up to 2 years because this enabled reliable estimation of the monthly fecundability. In younger women, the natural decline in fertility with female age would not have a significant effect over this time period.

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Subjects and methods

The study included 76 couples recruited from the Northern Regional Fertility Centre. All had unexplained infertility of between 3 and 14 years duration (median 5 years). The women's ages were between 25 and 35 years (median 30 years) and all had regular ovarian cycles of between 25 and 35 days. Ovulation was assumed to have occurred if progesterone concentrations in the luteal phase were greater than 20 nmol/l in three cycles during the preceding year. They were euthyroid (TSH between 1 and 6 mU/l) and normoprolactinaemic (<450 mU/l). Laparoscopy in all women had shown a normal uterus with mobile, patent fallopian tubes and mobile ovaries. Semen analysis in all husbands had been reported as normal by WHO standards (WHO 1987) on one occasion in the preceding year. The post coital test was normal as determined by the presence of more than five motile sperm per high power field ($\times 400$) in the presence of pre-ovulatory cervical mucus. For at least 3 months before treatment, the women recorded basal body temperature but no treatment was given and spontaneous pregnancy rates were recorded. The first 20 couples were offered three cycles of GIFT to enable calculation of the cumulative pregnancy rates and the remainder were offered two cycles. After GIFT, couples were monitored for up to 21 months.

The study was approved by Newcastle District Health Authority Ethics Committee.

GIFT procedure

On day 1 of the treatment cycle, ethinyl oestradiol, 35 μ g, plus levonorgestrel, 150 μ g, (Eugynon 30) tablets were prescribed for 10 days to induce withdrawal bleeding. On Day 14, the women were given human menopausal gonadotrophin (Pergonal) 150 IU FSH and 150 IU LH, daily intramuscularly and buserelin snuff, 200 μ g four times daily intranasally. Progress was monitored by transvaginal ultrasound scans and serum oestradiol estimations. On Day 21, if two or more follicles of >16 mm mean diameter were seen and the oestradiol concentration was >600 pmol/l per follicle, 5000 units of hCG were given intramuscularly. GIFT was performed between 34 and 36 h later.

Oocytes were retrieved laparoscopically. They were identified from aspirates of the follicular fluid and were kept in follicular fluid at 37°C until replacement. If the oocyte was not

obtained in the initial aspirate, follicles were flushed with Ham's F10 medium up to four times. Between two and four oocytes were transferred to the fallopian tube with, if possible, about 100 000 motile sperm. After 36 treatment cycles, the maximum number of oocytes transferred was reduced to three. For the transfer, a Rocket GIFT catheter was loaded with 5 μ l of Ham's F10 medium, 5 μ l of air, and about 40 μ l of medium containing oocytes and sperm. The contents of the catheter were then placed in one fallopian tube.

On the second and fourth days after treatment 2000 units of hCG were given to support the luteal phase.

Sperm preparation

Semen was produced by masturbation on the morning of the GIFT procedure. Semen volume, sperm count and motility were measured after liquefaction at 32°C. After centrifugation, motile sperm were extracted from the semen by overlaying Ham's F10 medium on to the sperm pellet. This was left for 30 min at 32°C after which the medium, then containing motile sperm, was carefully aspirated. Sperm count and motility were measured. The concentration was adjusted if possible to ensure insemination of approximately 100 000 motile sperm.

Pregnancy was diagnosed if the β hCG concentration was >25 units/l on day 12 after GIFT and was classified as either biochemical (no gestational sac on ultrasound scan 4 weeks after GIFT), blighted ovum (gestational sac seen but no fetal heartbeat) or clinical (fetal heartbeat seen).

Statistics

Life table analysis was performed on the data (Cramer *et al.* 1979). The starting point for study of spontaneous conception was the time of recruitment to the trial and for the GIFT study was the start of GIFT treatment. The end point in both cases was conception resulting in a live birth. Live birth rate was chosen as the end point because it was not possible to record all biochemical pregnancies after spontaneous conception. Furthermore a live birth is the desired end point by the patients.

Table 1. Life table analysis of spontaneous conceptions resulting in live births

Months	No. of couples	No. of pregnancies	Monthly pregnancy rates (%)	Cumulative proportion pregnant	5%–95% CI
0–3	76	5	2.2	0.06	0.02–0.14
3–6	46	2	1.4	0.10	0.04–0.19
6–9	43	4	3.1	0.18	0.06–0.34
9–12	37	0	0	0.18	0.06–0.34
12–15	36	1	0.9	0.21	0.06–0.39
15–18	30	1	1.1	0.23	0.06–0.46
18–21	18	0	0	0.23	0.06–0.46
21–24	12	1	2.8	0.30	0.06–0.48
Total	298*	14			

* Total number of cycles = $298 \times 3 = 894$.

Results

Spontaneous pregnancy rates

Before GIFT treatment, 12 pregnancies occurred in the 76 couples in the course of 366 cycles. Follow-up after GIFT revealed five further spontaneous clinical pregnancies from 528 cycles. Three of these 17 pregnancies resulted in a first trimester miscarriage and the other 14 were singleton and have ended successfully.

The data for each couple before and after GIFT treatment were added sequentially. Life-table analysis of these cumulative data is shown in Table 1. The average monthly fecundability (pregnancies resulting in live birth) was 0.021. The fecundability before GIFT was 0.03 and after GIFT it was 0.01 (difference $P < 0.04$).

Six couples decided after 3 months monitoring not to proceed to GIFT treatment for social reasons. They were excluded from the study after the initial monitoring.

GIFT pregnancy rates

There were 126 planned cycles of GIFT treatment for 53 couples. Only one operating session

per week was available and, consequently, 18 (16%) cycles were abandoned because of inadequate follicle growth by the required day. In nine cycles the couples decided not to proceed after their first GIFT attempt. Consequently 99 GIFT procedures were performed. Two of the 53 couples failed to reach oocyte retrieval because of persistent poor follicular growth. Thus 51 couples had at least one completed cycle of GIFT treatment.

Fourteen pregnancies resulted in a live birth. Life table analysis of the results are shown in Table 2. The average monthly fecundability was 0.14. There were ten singleton, three twin and one quadruplet pregnancies. In addition, there were 11 other pregnancies, of which one was ectopic, seven were biochemical and three resulted in a blighted ovum.

Cumulative pregnancy rates for GIFT and spontaneous conception are illustrated in Fig. 1.

Of the 10 couples who had an unsuccessful pregnancy after the first GIFT treatment, six conceived at the second attempt. On the other hand, of the 31 couples who failed to conceive at the first attempt, only three conceived at the second attempt.

Those couples for whom GIFT was successful

Table 2. Life table analysis of outcome of GIFT treatment (pregnancies resulting in live birth)

Months	No. of couples	No. of pregnancies	Monthly pregnancy rates (%)	Cumulative proportion pregnant	5%–95% CI
1	51	2	3.9	0.04	0.00–0.09
2	41	10	24.4	0.35	0.20–0.46
3	7	2	28.6	0.52	0.20–0.90
Total	99	14			

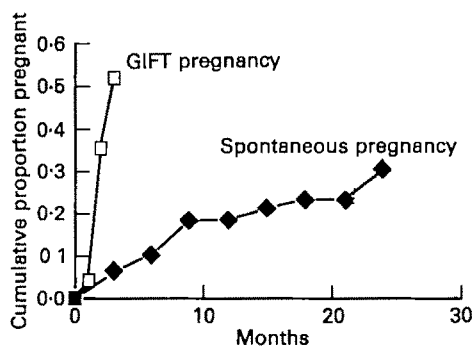


Fig. 1. Cumulative pregnancy rates resulting in live births following completed GIFT treatment cycles and cycles without treatment. Data from Tables 1 and 2

could not have been predicted from factors influencing the selection of couples for treatment, such as the woman's age, the duration of infertility and the semen criteria. Similarly, the numbers of follicles grown and of oocytes aspirated and transferred would not have predicted the outcome.

Discussion

The principal findings in this study are that the probability of having a baby following a single cycle of GIFT treatment is significantly higher than the probability in a spontaneous cycle despite the bias in favour of spontaneous conception in the study design. However, the cumulative conception rates suggest that if GIFT is to be a realistic treatment option, more than one cycle should be offered.

The spontaneous cumulative pregnancy rate in couples with unexplained infertility has been studied before and the rates are similar to those reported here. Collins & Rowe (1989) found a cumulative pregnancy rate (including unsuccessful pregnancies) of 27% at 2 years in couples infertile for 3 years or more. Lenton *et al.* (1977) also included unsuccessful pregnancies and reported that 43% had conceived at 9 years. In a more favourable group of couples, Templeton & Penney (1982) found the cumulative proportion with successful outcomes at 5 and 10 years was 53% and 79% (couples with secondary infertility of more than 2 years duration). Clearly, given enough time, the spontaneous cumulative preg-

nancy rate would be similar to three attempts of GIFT as reported here but since many women are over 30 years of age at the time of presentation, 'no treatment' would be unacceptable advice.

It could be argued that GIFT is successful in those couples who are most likely to conceive spontaneously. Our results offer some support for this theory since the spontaneous fecundability after GIFT was marginally lower than that before GIFT. However, the theory is not supported by the observation that GIFT success was not related to duration of infertility.

The pregnancy rates for GIFT in this study were low for the initial cycles although most of the unsuccessful conceptions occurred then. This is probably the result of our relative inexperience at the start of the study rather than a significant feature of the GIFT procedure. This can be seen in the success rates of the first 44 procedures (2 continuing pregnancies) compared with the final 55 procedures (12 continuing pregnancies).

Female age is the main prognostic factor for pregnancy in unexplained infertility (Collins & Rowe 1989) and is also important in GIFT success (Craft *et al.* 1988). Since no woman over the age of 35 was treated in this study, it is not surprising that no relation with age could be demonstrated.

We have assumed in the analysis that the fecundability is constant for all couples. The diagnosis of unexplained infertility is one of exclusion and it is therefore probable that subgroups exist with specific disorders and different prognoses for conception. Our results for the outcome of two GIFT cycles in the same women, although based on small numbers, suggest that there may be a subgroup of couples who have a higher chance of conceiving following GIFT. None of the factors we have measured has enabled us to identify these couples retrospectively. This is an important area for future investigation.

Acknowledgment

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Placental bed spiral arteries in the hypertensive disorders of pregnancy

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Abstract

Objective—The investigation of the histology of the placental bed spiral arteries in normal pregnancy and in pregnancies complicated by hypertension, with or without proteinuria.

Design—An observational study, based on women having caesarean sections for clinical reasons.

Subjects—17 normal pregnant women, 43 with gestational hypertension, of whom 39 had proteinuria, 17 with chronic hypertension, of whom 6 had proteinuria, and 5 with unclassified hypertension.

Interventions—Placental bed biopsies obtained during caesarean section

Main outcome measures—Histological appearance of sections stained with haematoxylin and eosin PAS and Lendrum's MSB.

Results—Biopsies containing spiral arteries were obtained from 6 normotensive and 44 hypertensive women. Trophoblastic invasion was present in 5 of the 6 normotensive biopsies but absent in the majority of those with hypertension. Subintimal proliferation was seen in all the normotensive biopsies but in only 8 of 28 from those with gestational hypertension and proteinuria. Other features seen predominantly or only in the hypertensive biopsies, in order of frequency, were medial hyperplasia, fibrin deposits, acute atherosclerosis, endothelial vacuolation and thrombosis.

Conclusion—Absence of physiological changes may not be peculiar to pre-eclampsia but may be associated or even a result of various forms of hypertension in pregnancy. Spiral arteries show a spectrum of changes in hypertensive pregnancies that do not appear to bear a clear-cut relation to the clinical signs.

Hypertensive disorders are a major complication of pregnancy and lesions of the spiral arteries play a key role in the pathophysiology of these disorders but the precise relation between

the histopathological changes in the placental bed and the different hypertensive disorders remains to be established. Until recently there was no agreed classification of the hypertensive

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disorders of pregnancy mainly due to the lack of knowledge of the nature of the underlying disease. Davey & MacGillivray (1988) introduced a new classification which groups patients with hypertension and/or proteinuria in pregnancy in clearly defined clinical categories. In this study we have attempted to relate the changes in the spiral arteries to the clinical condition of the patients.

The conversion of spiral arteries into uteroplacental arteries depends upon two waves of endovascular invasion by trophoblast in the first two trimesters of pregnancy. At term the trophoblastic cells are characteristically buried in the vessel walls and wrapped in fibrinoid material (Brosens *et al.* 1967; De Wolf *et al.* 1980; Pijnenborg *et al.* 1983). These changes are an essential part of placentation and the establishment of an adequate choriodecidual blood flow in normal pregnancy. In pre-eclampsia the second wave of trophoblastic invasion into the myometrial segments of the spiral arteries is believed to be inhibited and the normal physiological changes are absent (Brosens *et al.* 1972). The failure of the trophoblast invasion in the spiral arteries and the absence of the physiological changes has been regarded as responsible for the pathological changes in the placenta (Fox 1978) and the reduced uteroplacental blood flow in 'pre-eclampsia' (Browne & Veall 1953; McParland & Pearce 1988). However, a similar absence of physiological changes has been described in the spiral arteries of women with fetuses that were small for gestational age, both with and without 'pre-eclampsia' (Sheppard & Bonnar 1976; 1981; Brosens *et al.* 1977; Khong *et al.* 1986).

In the other hypertensive disorders of pregnancy the changes in the spiral arteries have been less well studied, although there have been reports of a small number of different hypertensive patients (Robertson *et al.* 1975; Brosens 1977; Sheppard & Bonnar 1981; Hustin *et al.* 1983; Khong *et al.* 1986; Frusca *et al.* 1989). Investigators have, however, used different terminology and classifications and have not adequately defined the clinical condition of the different patients from whom placental bed biopsies were obtained. The publication of the clinical classification developed by Davey & MacGillivray (1988) has presented a fresh opportunity to assess the placental bed changes and to relate to the clinical condition of the patient.

Subjects and methods

The study population consisted of women attending the Groote Schuur Hospital, Cape Town for antenatal and intrapartum care who were delivered by elective caesarean section. The women were recruited after informed consent was obtained. Two groups were studied (a) patients with non-proteinuric and proteinuric hypertension and (b) normotensive patients who acted as controls. Patients with underlying disorders were excluded. No attempt was made to match the patients in the hypertensive and control groups. Each of the patients was classified according to the criteria of Davey & MacGillivray (1988). Urinary protein estimations, platelet counts and renal function tests were performed on all the hypertensive patients.

Placental bed biopsy technique

A standardized technique for placental bed biopsies was used by all the surgeons. Immediately after the birth of the fetus the centre of the placenta was identified by inserting a hand into the uterus and palpating the placental site. The uterus was then delivered into the wound and, with the hand as a guide, a 22 gauge needle was inserted from the serosal surface through the uterus into the centre of the placental bed. The protruding end of the needle was identified and the accessibility of the placental bed assessed by the surgeon. In patients with an accessible placental bed, a second 22 gauge needle was inserted from the decidual surface into the uterus alongside the first marking needle which was then removed. Using a sharp scalpel a cone of decidual and myometrial tissues was excised around the second needle approximately 1–2 cm diameter and 1 cm deep. If necessary a pair of scissors was used to undercut the base of the cone and the freed specimen was placed in buffered formalin. The needle was left in the biopsy specimen to facilitate orientation and handling by the pathologist. The placental bed biopsy site was inspected for bleeding and if necessary a figure of eight suture inserted to secure haemostasis.

Histological techniques and assessment

After initial fixation the specimens were cut into thin slices of about 1 mm thickness in a direction perpendicular to the placental floor. After further fixation and embedding in paraffin wax, step-serial sectioning and staining of the speci-

mens (haematoxylin and eosin, PAS, and Lendrum's MSB) was performed using standard

Table 1. Clinical classification of hypertensive disorders of pregnancy

-
- A Gestational hypertension and/or proteinuria**
Hypertension and/or proteinuria developing during pregnancy, labour, or the puerperium in a previously normotensive nonproteinuric woman subdivided into
1. Gestational hypertension (without proteinuria)
 - a. Developing antepartum
 - b. Developing intrapartum
 - c. Developing postpartum
 2. Gestational proteinuria (without hypertension)
 - a. Developing antepartum
 - b. Developing intrapartum
 - c. Developing postpartum
 3. Gestational proteinuric hypertension (pre-eclampsia)
 - a. Developing antepartum
 - b. Developing intrapartum
 - c. Developing postpartum
- B. Chronic hypertension and chronic renal disease**
Hypertension and/or proteinuria in pregnancy in a woman with chronic hypertension or chronic renal disease diagnosed before, during, or after pregnancy subdivided into
1. Chronic hypertension (without proteinuria)
 2. Chronic renal disease (proteinuria with or without hypertension)
 3. Chronic hypertension with superimposed pre-eclampsia (proteinuria developing during pregnancy in known chronic hypertension)
- C. Unclassified hypertension and/or proteinuria**
Hypertension and/or proteinuria found either
- (a) At first examination after 20 weeks (140 days) in a woman without known chronic hypertension or chronic renal disease or
 - (b) during pregnancy, labour, or the puerperium where information is insufficient to permit classification and subdivided into
 1. Unclassified hypertension (without proteinuria)
 2. Unclassified proteinuria (without hypertension)
 3. Unclassified proteinuric hypertension
- D Eclampsia**
The occurrence of generalized convulsions during pregnancy, during labour, or within 7 days of delivery and not caused by epilepsy or other convulsive disorders.
-

histological techniques. Biopsies of the placental bed were considered adequate when interstitial trophoblastic giant cells and at least one spiral artery were present. Biopsies from the marginal areas of the placental bed, as indicated by accumulated glands in the decidua, were regarded as unrepresentative and inadequate, even if trophoblastic giant cells were present. Attention was concentrated on the myometrial portion of the placental bed as the most important changes occur at this site and decidual tissue was often limited.

Results

General observations

The clinical classification, demographic characteristics and perinatal outcome of the patients are set out in Tables 1, 2 and 3. Biopsies were obtained from 65 hypertensive patients of which 44 (68%) were adequate and 17 from normotensive patients of which 6 (35%) were adequate (Table 4). The number of spiral arteries found was 1 in 20, 2 in 22 and 3 in 8 biopsies. The occurrence and degree of the trophoblastic invasion and of the physiological changes of the spiral arteries was carefully assessed. The presence of perivascular trophoblastic cells (interstitial trophoblastic giant cells in the direct vicinity of the arteries) was also recorded.

The occurrence and degree of the physiological changes was confirmed using PAS and Lendrum's MSB staining to reveal fibrinoid material more clearly (Fig. 1). Physiological changes may be present in the whole circumference or may be restricted to one sector of a vessel. Sometimes only a few isolated trophoblastic cells can be seen (Fig. 2). Vessels where physiological changes were restricted to less than 50% of the circumference were referred to as arteries with partial physiological changes. Cushions of fibrous tissue were often found in the intima and, notably, in arteries with only partial physiological changes, the cushions were invariably found in the intima overlying the fibrinoid material and the trophoblastic cells buried in the vessel wall.

In the absence of trophoblast and physiological changes any aberrations from normal histology were carefully noted. One such feature was the occurrence of endothelial vacuolation in a number of biopsies. Furthermore, apart from intimal thickening, the media often showed disorganization and sometimes a marked hyper-

Table 2. Demographic data

	Classification						
	N	GH	GPH	CH	CH+GPH	UH	UPH
Number of patients	17	4	39	11	6	1	4
Age years							
Mode	28	33	20	34	29	35	28
(Range)	(19-36)	(22-39)	(16-45)	(28-37)	(26-35)		(21-35)
Parity							
Mode	2	3	0	1	2	3	2
(Range)	(0-7)	(1-4)	(0-10)	(0-5)	(1-3)		(0-5)

Key: N = normotensive, GH = gestational hypertension, GPH = gestational proteinuric hypertension, CH = chronic hypertension, CH+GPH = chronic hypertension with superimposed gestational proteinuric hypertension, UH = unclassified hypertension, UPH = unclassified proteinuric hypertension.

plasia, leading to a narrowing or even a virtual obliteration of the arterial lumen (Fig. 3).

Two other vasculopathies of the spiral arteries were encountered, namely, acute atherosclerosis and arterial thrombosis. Acute atherosclerosis, which is characterized by fibrinoid necrosis and infiltration of the media with foam cells and leucocytes (Robertson *et al* 1967), only occurred in arteries in which trophoblastic invasion and physiological changes were absent (Fig. 4). Acute atherosclerosis was, however, sometimes associated with

subintimal and medial hyperplasia. Arterial thrombosis was only found in two biopsies.

Histological characterization of the spiral arteries

The characteristic histological features of the myometrial segments of the spiral arteries in the different clinical categories are summarised in Tables 4, 5 and 6. The number of biopsies in each category that show either partial or complete

Table 3. Clinical data at delivery and perinatal outcome

	Classification						
	N	GH	GPH	CH	CH+GPH	UH	UPH
Number of patients	17	4	39	11	6	1	4
Diastolic blood pressure (mmHg)	75.0 (6.4)	102.5 (17.1)	103.0 (11.6)	92.7 (8.2)	105.0 (8.4)	110	97.5 (9.6)
Proteinuria (mg/24 h)	—	—	5263 (4243)	—	2215 (1842)		7075 (3382)
Serum urate (mmol/l)	—	0.28 (0.02)	0.41 (0.12)	0.34 (0.07)	0.34 (0.05)	0.24	0.37 (0.08)
Serum creatinine (mmol/l)	—	74.7 (8.5)	78.5 (16.6)	70.3 (11.0)	73.5 (19.7)	70.0	88.0 (25.8)
Platelet count	—	240 (53)	234 (70)	273 (108)	289 (134)	463	248 (102)
Gestational age at delivery (weeks)	37.7 (2.6)	34.2 (3.4)	31.4 (3.0)	34.6 (3.9)	32.0 (3.9)	32	29.7 (2.1)
Birthweight (g)	3127 (762)	2065 (913)	1503 (578)	2385 (893)	1753 (764)	1050	1377 (597)
Placental weight (g)	579 (145)	390 (179)	340 (114)	522 (155)	425 (112)	250	387 (137)
No. of SGA babies*	2	1	22	3	3	1	1

Results are expressed as means (SD). See Table 2 for key to abbreviations.

* Small for gestational age: <25th centile weight for gestational age on Lubchenko charts

physiological changes in one or more spiral arteries are shown in Table 5. Table 6 gives the total number of biopsies showing the other histopathological features in at least one spiral artery in each clinical category.

Normotensive control. The six biopsies all showed normal trophoblastic invasion and physiological changes. In one biopsy physiological changes were present in one of the two spiral arteries but absent in the other and in another biopsy the artery showed physiological changes and endothelial vacuolation. Three biopsies showed fibrin deposition on MSB staining but there were no marked perivascular accumulations of trophoblastic giant cells around any of the arteries and no vasculopathies. A striking feature in all the biopsies was the marked subintimal thickening in the areas of the vessel walls overlying the physiological changes.

Gestational hypertension (GH) and gestational proteinuric hypertension (GPH). The spiral arteries from these patients all showed severe limitation of the normal physiological changes. In two patients with GPH one of two arteries showed complete absence of physiological changes whereas the other artery showed normal trophoblastic invasion. In six patients with GPH partial physiological changes were observed and in three of the biopsies there were other arteries that did show complete absence of physiological changes. Of the 29 biopsies from women of the two groups 13 showed medial hyperplasia, 10 fibrin deposits, 9 subintimal proliferation and 4 endothelial vacuolation of the spiral arteries. Perivascular trophoblastic giant cells were present in nine women. Acute atherosclerosis which is believed to be a characteristic lesion of the spiral arteries in 'pre-eclampsia' was only found in 6 of the 28 patients with GPH and one biopsy in the same group showed arterial thrombosis.

Chronic hypertension (CH) and with superimposed pre-eclampsia (CH+GPH). Of the 12 biopsies in these two groups only two showed the normal physiological changes and one patient with CH+GPH showed partial physiological changes of the spiral arteries. Endothelial vacuolation was found in eight, medial hyperplasia in six and fibrin deposits in five of the biopsies. Perivascular trophoblastic giant cells were only observed around arteries without physiological

changes. Acute atherosclerosis was found in three of the five biopsies from women with chronic hypertension and superimposed pre-eclampsia.

Unclassified hypertensive disorders (UH and UPH). These groups include all patients in whom it was uncertain whether the disorder had developed in pregnancy and was 'gestational' or pre-existed pregnancy and was 'chronic'. All three patients in this category showed absence of physiological changes. Endothelial vacuolation occurred twice, and subintimal proliferation, medial hyperplasia and fibrin deposits were each found in one woman. Perivascular trophoblastic giant cells were observed in the three patients. One showed acute atherosclerosis and another thrombosis of the spiral arteries, and both were from the UPH group.

Discussion

The changes in the spiral arteries during pregnancy do not appear to fall into a clear-cut pattern or to be specific to a hypertensive disorder such as 'pre-eclampsia'. Trophoblastic invasion of the myometrial segments of the spiral arteries was inhibited in virtually all the pregnant women with hypertension in contrast to the normotensive patients in whom physiological changes were nearly always observed. In the present series normal physiological changes were only seen in 2 of the 44 hypertensive patients, both of whom had chronic hypertension without proteinuria. Brosens (1977) stated that physiological changes occur in the spiral arteries of women with essential hypertension in the same way as in normal pregnancy. However, Robertson *et al.* (1975) noted that in some women with essential hypertension the changes 'seemed less than adequate' and other investigators reported the absence of physiological changes in such cases (Sheppard & Bonnar 1981; Frusca *et al.* 1989). Women with hypertension in pregnancy, including patients with chronic hypertension, do not form a homogenous group and the findings in the spiral arteries illustrate the need for a better understanding of the underlying aetiological and pathological factors.

The timing and extent of the trophoblastic invasion may be more variable than is usually assumed. In normal pregnancy about 32% of spiral arteries have undergone physiological changes by 16 to 18 weeks (Pijnenborg *et al.* 1983) but almost all the 100 to 150 arteries show

Table 4. Numbers of placental bed biopsies within each category of hypertensive disorders of pregnancy

Placental biopsies	Classification						
	N	GH	GPH	CH	CH+GPH	UH	UPH
Total no.	17	4	39	11	6	1	4
No. with spiral arteries	6	1	28	7	5	1	2

See Table 2 for key to abbreviations.

physiological changes by term. This suggests that the trophoblastic invasion of the myometrial segments and the development of physiological changes in the spiral arteries continues throughout pregnancy and is not confined to the first two trimesters. Placental bed biopsies unfortunately can only be taken towards the end of pregnancy when caesarean section is performed. It is therefore difficult to know whether the inhibition of trophoblastic invasion precedes, accompanies or follows the development

of hypertension in pregnancy. The present study has also shown that the trophoblastic invasion and the physiological changes of the spiral arteries in hypertensive pregnancies may be partial and incomplete. The inhibition of trophoblastic invasion of spiral arteries in the hypertensive disorders of pregnancy is therefore by no means a uniform process or an 'all or none' phenomenon.

The presence of interstitial giant cells in the direct vicinity of the spiral arteries was particularly obvious in the biopsies from hypertensive

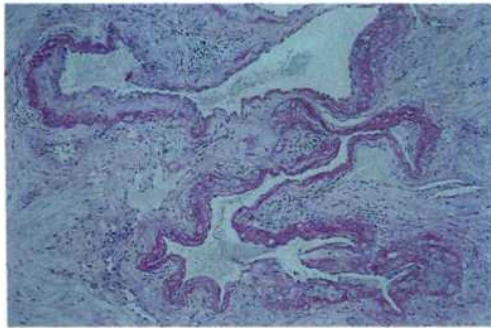


Fig. 1. Myometrial spiral artery of a normotensive woman, showing the normal physiological changes of pregnancy. The vessel wall is replaced by trophoblastic cells buried in a PAS-positive fibrinoid material (PAS×25).

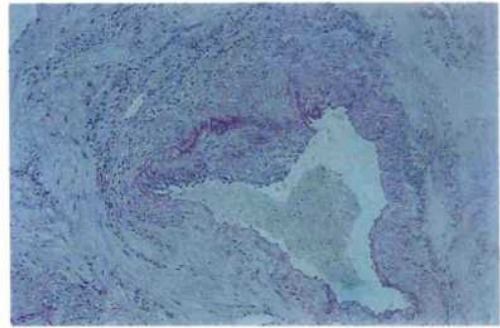


Fig. 2. Myometrial spiral artery of a patient with gestational proteinuric hypertension, showing a marked reduction of physiological changes. Only a few trophoblastic cells within some fibrinoid material are revealed using PAS-staining (PAS×25).

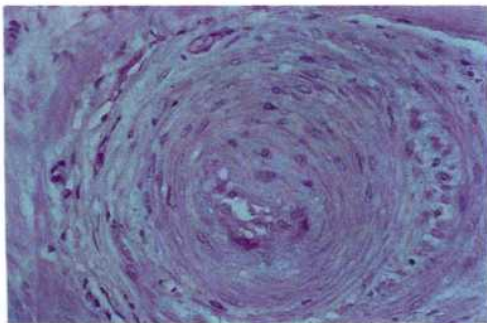


Fig. 3. Myometrial spiral artery of a patient with gestational proteinuric hypertension, showing complete absence of physiological changes and hyperplasia of the media (H&E×100).

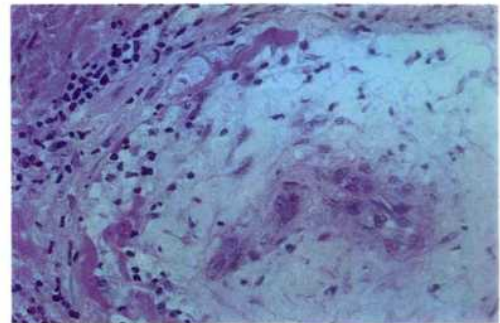


Fig. 4. Acute atherosclerosis in a myometrial spiral artery of a patient with chronic hypertension and superimposed pre-eclampsia (H&E×100).

Table 5. Numbers of biopsies with and without physiological changes in spiral arteries in each of the categories of hypertensive disorders of pregnancy

	Classification						
	N	GH	GPH	CH	CH+GPH	UH	UPH
Total with spiral arteries	6	1	28	7	5	1	2
Physiological changes							
Present in all arteries							
Complete	5	0	0	2	0	0	0
Partial	0	0	3	0	1	0	0
Absent in all arteries	0	1	20	5	4	0	1
Absent in some arteries							
+Complete	1	0	2	0	0	1	1
+Partial	0	0	3	0	0	0	0

See Table 2 for key to abbreviations.

women where inhibition of endovascular trophoblast invasion had occurred. Analogous observations have been reported by Gerretsen *et al.* (1983) but are difficult to interpret. A close association between the presence of perivascular trophoblast and early vascular changes that precede endovascular trophoblast invasion and the elaboration of physiological changes has been demonstrated in early pregnancy specimens (Pijnenborg *et al.* 1983). However, it is difficult to understand why in hypertensive cases such a relation between perivascular trophoblast and the development of physiological changes has been lost at a certain stage during pregnancy.

The development of physiological changes is associated with a severe disruption of the vessel wall so that the normal haemostatic process should be activated, eventually even leading to thrombosis. In our series arterial thrombosis was

only observed in two patients, both with proteinuric hypertension. Fibrin deposits, as revealed by MSB staining, were found not only within the fibrinoid material associated with physiological changes but also in noninvaded spiral arteries in a number of women with hypertension. These observations suggest that leakage into the vessel wall may have occurred at a particular stage during pregnancy. In hypertensive women this feature was always associated with either subintimal thickening or acute atherosclerosis in the artery wall.

Acute atherosclerosis of the spiral arteries has been considered as a virtually pathognomonic lesion of 'pre-eclampsia' (Robertson *et al.* 1975). Sheppard & Bonnar (1981) criticised this claim because of the finding of identical lesions in the spiral arteries of the decidua and basal plate in normotensive women with fetal growth retardation.

Table 6. Histopathological features of spiral arteries in placental bed biopsies in the different categories of hypertensive disorders of pregnancy

	Classification						
	N	GH	GPH	CH	CH+GPH	UH	UPH
No. of biopsies with spiral arteries	6	1	28	7	5	1	2
Endothelial vacuolation	1	0	4	6	2	0	2
Subintimal proliferation	6	1	8	0	1	1	0
Medial hyperplasia	0	1	12	3	3	1	0
Thrombosis	0	0	1	0	0	0	1
Acute atherosclerosis	0	0	6	0	3	0	1
Fibrin deposits	3	0	10	3	2	0	1
Perivascular trophoblast	0	1	8	2	1	1	2

See Table 2 for key to abbreviations.

dation. In our study acute atherosclerosis was only found in the myometrial segments of spiral arteries from patients with proteinuric hypertension and not necessarily in all such cases. This is in agreement with other studies (Sheppard & Bonnar 1981; Hustin *et al.* 1983) and is to be expected in view of the focal and scattered nature of the lesions (Khong *et al.* 1987) and the small number of arteries present in any placental bed biopsy.

Other observations in the present series include the presence of endothelial vacuolation which appeared to be particularly common in women with chronic hypertension. No explanation of the phenomenon can be given at the moment. Medial hyperplasia and subintimal proliferation were observed in the spiral arteries of hypertensive patients which, often, resulted in almost total occlusion of the vessels. However, subintimal thickening occurred not only in non-invaded arteries of hypertensive patients, but also in arteries with physiological changes from normotensive women. Moreover, the observation that subintimal thickening in arteries with partial physiological changes occurred in the form of 'cushions' situated immediately over the areas of trophoblast invasion suggests that proliferation can occur not only as a response to high blood pressure but also as a reaction to underlying trophoblastic cells, possibly as a repair phenomenon. Tissue repair mechanisms may play a role in restricting trophoblast invasion. Therefore, in women with hypertension in pregnancy there may be an over-reaction by the arteries to the physiological trophoblastic invasion.

The clinical and methodological limitations of placental bed biopsy make this a difficult area of study but further investigations are required. Histochemical and immunohistochemical studies may help to elucidate the processes involved in this major part of placental pathology of pregnancy and of the aetiology of the hypertensive disorders of pregnancy.

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The variation of endometrial response to a standard hormone replacement therapy in women with premature ovarian failure. An ultrasonographic and histological study

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Summary. The endometrial response to a standard hormone replacement therapy in 18 women with premature ovarian failure was examined by serial ultrasonographic measurement of endometrial thickness and histological study of endometrial biopsy taken on day 19 of the cycle. Women with idiopathic ovarian failure ($n = 10$) had significantly better response than women with Turner's syndrome ($n = 4$), whereas women with premature ovarian failure associated with previous chemotherapy ($n = 4$) had an intermediate response. These observations suggest that the endometria of women with Turner's syndrome responded suboptimally to steroid hormones. However, all endometrial biopsies studied revealed secretory changes. Overall, the results of histological dating of endometrial biopsy were found to be positively correlated with endometrial thickness on day 19 of the cycle ($r = 0.72$, $P < 0.01$). The plasma concentration of oestradiol on days 15, 19 and 29 of the artificial cycle were found to be significantly higher than those on the corresponding days of the natural cycle.

Premature ovarian failure, sometimes referred to as premature menopause, may be defined when ovarian function ceases before the age of 40 (Coulam *et al.* 1986; Mattison *et al.* 1984). Ovarian fail-

ure is established when amenorrhoea is associated with low oestradiol and high gonadotrophin concentrations in plasma. Women with this condition require hormone replacement therapy (HRT) to alleviate symptoms of oestrogen deficiency such as dry vagina, breast atrophy and to prevent osteoporosis and coronary atherosclerosis. Some of them also wish to seek treatment for infertility, which is an inevitable consequence of premature ovarian failure. The first successful pregnancy in a woman with premature ovarian failure after treatment with sequential HRT and donor oocyte was reported by Lutjen *et al.* (1984). Since then, a number of other HRT regimens capable of producing normal endometrial development or supporting implantation have been reported (Navot *et*

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al. 1986; Rosenwaks, 1987; Asch *et al.* 1988; Serhal & Craft, 1989).

While it is still a matter of debate which of these HRT regimens is superior, there is surprisingly little published information to show whether or not the endometrial response of women with premature ovarian failure to a given HRT regimen is consistent or predictable. A retrospective study by Fraser *et al.* (1989) on the endometrial response of post menopausal women to combined oestrogen/progestogen HRT noted a wide inter-subject variation. The present prospective study was designed (a) to examine the variability of endometrial response of women with premature ovarian failure to a standard HRT regimen; and (b) to analyse the possible factors affecting the observed variability.

Subjects and methods

A total of 18 women with premature ovarian failure attending the gynaecological outpatient clinic at the Jessop Hospital for Women were recruited to the study. Premature ovarian failure was defined as amenorrhoea of 6 months or more, associated with persistently low plasma oestradiol (<100 pmol/l) and elevated plasma follicle stimulating hormone (FSH) (>20 iu/l), in a woman under 40 years of age (Mattison *et al.* 1984). All the subjects recruited had a chromosome analysis, and blood tests for antiovarian antibody, thyroid function and prolactin assay.

The 18 women were classified into three categories according to the cause of premature ovarian failure. Group 1 included 10 women with idiopathic ovarian failure. Group 2 included four women who had had chemotherapy for malignant diseases. Two of them had been treated for leukaemia by chemotherapy, total body irradiation and marrow transplant, the other two had had lymphoma treated by chemotherapy alone, without any irradiation. The third group included four women with Turner's syndrome (XO).

None of the women in the study had antiovarian antibody, all had normal thyroid function and normal prolactin levels. One of the ten women in group 1 had a family history of premature ovarian failure (involving two sisters). One woman in group 1 and the four women in group 3 had primary amenorrhoea, the others all had secondary amenorrhoea.

Table 1 details the age, body weight, height, body mass index and duration of ovarian failure in the three groups. The four women with Turner's

syndrome (group 3) were the shortest and weighed least, but there was no significant difference in the body mass index between the three groups.

The duration of HRT ranged from 1 month to 12 years (median 7 months) in group 1; 2 months to 5 years (median 2.5 years) in group 2; and 5 to 12 years (median 9 years) in group 3. Most of the women had had HRT far more than 6 months, except for four in group 1 (3 had 1 month and 1 had 2 months) and a further woman in group 2 (2 months). The pre-study plasma oestrogen concentrations were below the sensitivity of the assay (<29 pmol/l) in 4 of the ten women in group 1 and between 33 and 89 pmol/l in the other six. In group 2 pre-study plasma oestradiol concentrations were below the sensitivity of the assay in two women and measured 79 and 94 pmol/l, respectively, in the other two. In group 3 the oestradiol concentration was below the sensitivity of the assay in three of the four women, and measured 94 pmol/l in the remaining woman.

Each of the subjects recruited underwent the following protocol: (a) a pre-study cycle, in which Cyclo-Progynova 2 mg (Schering, Sussex) was administered (oestradiol valerate 2 mg daily for 11 days followed by oestradiol 2 mg plus norgestrol 500 µg daily for 10 days); (b) a study cycle, which started 7 days after the cessation of Cyclo-Progynova therapy, in which a standard HRT regimen (Navot *et al.* 1986) was administered (Table 2). Observations during the study cycle included: plasma samples (on days 1, 15, 19 and 29 of the cycle) for FSH, luteinizing hormone (LH), oestradiol and progesterone assay; ultrasonographic measurement of endometrial and uterine thickness on days 1, 15 and 19 of the cycle; an outpatient endometrial biopsy on day 19 of the cycle.

Hormone assay

Progesterone and oestradiol were assayed by non-extraction, solid phase radioimmunoassay (RIA) using ¹²⁵I as a marker (Diagnostic Products Limited, Abingdon, Oxon). For progesterone the sensitivity of the assay was 0.16 nmol/l and the mean intra- and inter-assay coefficients of variation were 7.2% and 7.9%, respectively. For oestradiol the sensitivity of the assay was 29 pmol/l and the mean intra- and inter-assay coefficients of variation were 5.4% and 6.4%, respectively. LH and FSH were estimated by immunoradiometric assay (IRMA), incorporating two high affinity monoclonal antibodies, using ¹²⁵I (Serono Diagnostic Limited,

Table 1. Characteristics of the 18 women with premature ovarian failure in three categories

Variable	Group 1 (idiopathic) (n = 10)		Group 2 (chemotherapy) (n = 4)		Group 3 (Turner's syndrome) (n = 4)	
Age (years)	31.3	(3.5)	29.8	(6.0)	26.3	(2.4)
Body weight (kg)	63.8	(8.3)	64.1	(12.4)	49.2	(5.6)*
Height (m)	1.66	(0.07)	1.61	(0.04)*	1.48	(0.04)*
Body mass index (kg/m ²)	23.1	(2.5)	24.7	(4.6)	22.4	(1.8)
Duration of ovarian failure (years)	7.1	(6.2)	7.8	(5.1)	13.3	(2.4)

Results are means (SD) values.

*Significantly different between groups 3 and 1 and between groups 2 and 3; $P < 0.01$ (two-sample Student's *t*-test). There was no significant difference between groups 1 and 2 for any of the variables.

Surrey). For LH the sensitivity of the assay was 0.15 mIU/ml. The mean intra- and inter-assay coefficients of variation were 5.0% and 5.5%, respectively. For FSH the sensitivity of the assay was 0.25 mIU/ml. The mean intra- and inter-assay coefficients of variation were 2.0% and 3.3%, respectively.

Ultrasonography

This used a transabdominal real-time scanner (Combison 320, Kretztechnik, Zipf, Austria). The maximum thickness of the uterus and endometrium on longitudinal section were measured three times, and the mean value was used for subsequent calculation. Ultrasonography was performed by two observers, with an inter-observer coefficient of variation $< 8.2\%$. The endometrium and myometrium and the result represents the two layers of endometrium.

Endometrial biopsy

Endometrial biopsies were obtained from outpatients using a Sharman's curette (Downs Sur-

gical Limited, Sheffield, UK). A single endometrial specimen was obtained from the fundus and upper part of the body of the uterus. Each specimen was fixed immediately in 2% glutaraldehyde in cacodylate buffer (pH 7.4) for 4–6 h. It was then washed in buffer, dehydrated and embedded in JB-4 (Polysciences, Inc., Warrington, PA, USA), a plastic polymer. The specimen was sectioned at 2 μ m, and the sections were stained with acid fuchsin and toluidine blue for light microscopy.

All the endometrial biopsies were dated histologically by one observer using two different methods: the traditional dating criteria (Noyes *et al.* 1950) and morphometry as described by Li *et al.* (1988).

Ethical aspects

Informed consent was obtained from each woman and approval for this study has been obtained from the hospital ethics committee in Sheffield.

Statistics

The results between groups (subjects or days) were compared using the 2-sample *t*-test after log transformation of the hormone data. As multiple comparisons were made in most cases (between 3 groups), a *P*-value of < 0.01 was considered significant. Similarly, for the correlation analysis between histological dating and the various clinical, endocrinological and ultrasonographic observations, a *P*-value of < 0.01 was considered significant. Histological dating was based on morphometric criteria as these give better results than those based on the traditional dating (Li *et al.* 1989).

Results

All endometrial biopsy specimens showed secre-

Table 2. Hormone replacement therapy regimen proposed by Navot *et al.* (1986)

Day of cycle	Oral oestradiol valerate (mg)	Intramuscular progesterone (mg)
1–5	1	—
6–9	2	—
10–13	6	—
14	2	—
15–16	2	25
17	2	50
18–26	4	50
27–28	1	25

tory activity either within the gland cells or the uterine lumina. The results of the measurements on uterine thickness, endometrial thickness and histological dating by both the traditional criteria and morphometry are shown in Figure 1. The women with Turner's syndrome (group 3) had the smallest uterine thickness (days 1, 15 and 19), endometrial thickness (days 15 and 19) and the least advanced histological dating (both traditional criteria and morphometry), whereas group 1 was similar to group 2.

Two of the four women in group 2 had poor peripheral veins as a result of previous chemotherapy, so that blood samples were not obtained. Otherwise, the hormonal profiles throughout the study cycle (days 1, 15, 19 and 29) were similar in the three groups and the combined hormonal profiles of the three groups of women ($n = 16$) are shown in Fig. 2.

Correlates of histological dating

The results of histological dating (by morphometry) were correlated with the ultrasonographic

measurements, the body mass index, age and duration of premature ovarian failure. There was a significant correlation ($P < 0.01$) between histological dating and endometrial thickness on day 19 of the cycle ($r = 0.72$, $P < 0.01$) but there were no significant correlations between histological dating and the other ultrasonographic and clinical observations. The results of histological dating by morphometry were significantly correlated with those obtained using standard dating criteria ($r = 0.68$, $P < 0.002$).

Endocrinological profiles: comparison with natural cycles

The mean plasma oestradiol concentration was 1800 pmol/l on day 15 and 2265 pmol/l on day 19. These results are comparable to those reported by Navot *et al.* (1986). Assuming that days 15 and 19 of the artificial cycle correspond to days LH+1 and LH+5 of the natural cycle, the plasma oestradiol concentrations on these 2 days of the artificial cycle are significantly higher (about four times) than those of the corresponding days of the natural

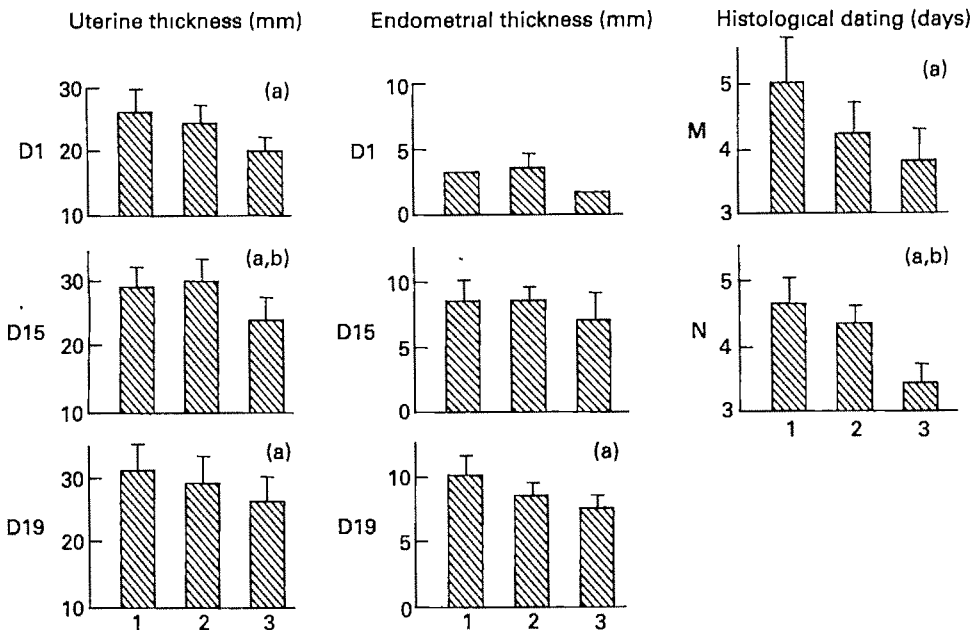


Fig. 1. Uterine and endometrial thickness on day 1 (D1), day 15 (D15) and day 19 (D19) of the artificial cycles, and histological dating by criteria of Noyes *et al.* (1950) (N), and morphometry (Li *et al.* 1988) (M), on endometrial samples collected on day 19 of the cycle, in women with premature ovarian failure receiving a standard hormone replacement regimen. The bar represents the mean, the vertical line represents the standard deviation. Group 1 includes 10 women with idiopathic ovarian failure, group 2 includes four women who had had chemotherapy and group 3 includes four women with Turner's syndrome. There were no significant differences between groups 1 and 2; (a), significant difference ($P < 0.01$) between groups 1 and 3; (b), significant difference ($P < 0.01$) between groups 2 and 3.

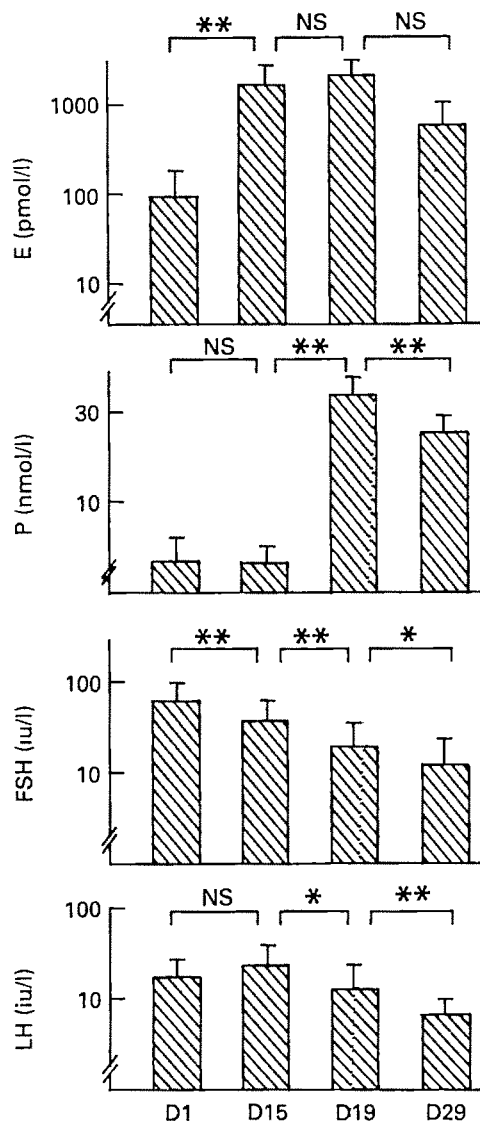


Fig. 2. Plasma concentrations of oestradiol (E), progesterone (P), follicle stimulating hormone (FSH) and luteinizing hormone (LH) on day 1 (D1), day 15 (D15), day 19 (D19) and day 29 (D29) of the artificial cycle in 16 women with premature ovarian failure receiving the hormone replacement therapy. The bar represents the geometric mean, with vertical line representing the standard deviation. Note the log vertical axis.

* $P < 0.01$; ** $P < 0.001$; NS, not significant. (2-sample *t*-test on log transformed data).

cycle (Lenton *et al.* 1982). The progesterone profiles were comparable to those of the natural cycles.

Discussions

In this study, the response of the endometrium in women with premature ovarian failure to a standard HRT regimen was analyzed. Endometrial development in women with Turner's syndrome was significantly retarded compared with that in women with idiopathic premature ovarian failure. The reason for this observation is not known. Although the women with Turner's syndrome were shorter and lighter than those in the other group these factors are unlikely to contribute to the observed difference between the two groups, because the body mass index was similar in the two groups.

As all the women received the same doses of oestrogen and progesterone, and had similar plasma concentrations of oestradiol and progesterone, it is also unlikely that the difference in endometrial response was due to varying degrees of endometrial stimulation. On the other hand, it is possible that the endometria of women with Turner's syndrome respond suboptimally to steroid hormones. The same may be true of the response of the breasts, as it is generally difficult to achieve breast development beyond Tanner stage 3 in women with Turner's syndrome. It would be useful to compare the concentrations of endometrial steroid hormone receptors between women with Turner's syndrome and those with other causes of premature ovarian failure, to establish whether the observed retardation of endometrial development in women with Turner's syndrome is associated with a reduced concentration of endometrial steroid receptors. Although successful pregnancies have been reported in women with Turner's syndrome after treatment with HRT and donor oocytes (Salat-Baroux *et al.* 1988), it will also be of interest to compare the pregnancy rate in these women with the rate in women with other causes of premature ovarian failure, to determine if the observed difference in endometrial development is of functional and prognostic significance.

Although, the number of women in groups 2 and 3 was small (only four women in each group) we found statistically highly significant differences in a number of measurements, between groups 1 and 3. This suggests that the difference between the two groups is important. In contrast, no differences were apparent between groups 1 and 2, nor between groups 2 and 3. A larger study would be required to test the hypothesis that there is a small difference in endometrial response between groups 1 and 2, or between groups 2 and 3. The

results shown in Fig. 1 suggest that the endometrial response in group 2 was probably intermediate between groups 1 and 3.

Fraser *et al.* (1989) analysed the endometrial response in post-menopausal women receiving 0.625 mg or 1.25 mg of equine oestrogens and one of three progestogens at different doses, they found a wide inter-subject variation in response and none of the nine progestogen dose regimens induced secretory changes consistently in every woman. However, in our study involving 18 women, despite the significant variation in endometrial response between the different groups, we were able to demonstrate secretory changes in the endometrium in all those studied.

Clinical implications

The observed variation in the endometrial response in women with premature ovarian failure has a number of clinical implications. First, women with premature ovarian failure should not be taken to represent a homogeneous population. A satisfactory response in some women to a HRT regimen may not necessarily imply the same in others, individual monitoring of the response is important. Second, in clinical trials which compare two or more HRT regimens, a cross-over design may be more appropriate than a cohort design, as the former reduces the variance of results due to individual difference in endometrial response. Third, our results suggest that the dose of oestrogen in the HRT regimen proposed by Navot *et al.* (1986) may be too high. It may be possible to further improve endometrial development in artificial cycles by reducing the dose of oestrogen administered.

Acknowledgment

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The place of oophorectomy at vaginal hysterectomy

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Summary. A series of 740 vaginal hysterectomies with attempted vaginal oophorectomy is presented and compared with 700 vaginal hysterectomies without oophorectomy. Vaginal oophorectomy was successful in 94% of the patients. Factors influencing the success include obesity, nulliparity, decreased vaginal access and space, lack of uterine descent, increased uterine size and tubo-ovarian disease. These have been analysed and the recognition and management of technical difficulties are described. There was no morbidity attributable to the vaginal oophorectomy. With experience and appropriate technique suitable women can be offered prophylactic oophorectomy at the time of vaginal hysterectomy.

The late presentation and poor response to treatment of ovarian carcinoma are the main reasons for prophylactic oophorectomy in postmenopausal woman undergoing hysterectomy. In a survey of fellows and members of the RCOG on the practice of prophylactic oophorectomy at the time of hysterectomy, Jacobs & Oram (1989) found that 52% perform oophorectomy in patients over 49 years of age and 85% perform routine oophorectomy in postmenopausal patients. These results refer almost entirely to abdominal rather than vaginal oophorectomy. Prophylactic oophorectomy is much less frequently performed during vaginal hysterectomy because of technical difficulty in securely ligating the ovarian vessels.

The author's experience in a series of 740 vaginal hysterectomies with attempted vaginal oophorectomy is presented and compared with 700 vaginal hysterectomies without oophorectomy to analyse the favourable and unfavour-

able factors. The techniques used to overcome surgical difficulties are discussed.

Subjects and methods

The 1440 women in this analysis had their vaginal hysterectomies between 1977 and 1988 in private clinics, in 740 vaginal oophorectomy was attempted at the time of hysterectomy.

The women in both groups were comparable in age and parity. The indications for hysterectomy were similar in the two groups and are shown in Table 1.

Vaginal hysterectomy was not attempted in any woman with a uterus over 12 weeks in size. Removal of both ovaries was planned whenever this would have been performed if the hysterectomy was to have been abdominal. No hysterectomy was performed solely for prophylactic removal of ovaries. Patients requiring oophorectomy for reasons other than prophylaxis were not included in this study.

Ovaries were not removed in the comparison group because at the time of their operation (1977-1983), it was not policy to advise this procedure at vaginal hysterectomy. Since then, the ovaries are not removed prophylactically if the woman does not wish it, if she has ischaemic heart disease, hypertension or if she is reluctant

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Table 1. Characteristics of the women having vaginal hysterectomy with or without oophorectomy

Variable	Patients at vaginal hysterectomy	
	Oophorectomized (<i>n</i> = 740*)	Not oophorectomized (<i>n</i> = 700)
Age (years)		
< 46	24	527
46–50	504	108
51–60	158	43
≥61	54	22
Parity		
Nulliparous	72	91
<4	449	406
≤4	219	203
Indications for hysterectomy		
Dysfunctional bleeding	530	471
Fibroids	126	157
Uterine prolapse	76	61
Cervical polyp	4	9
Carcinoma in situ (cervix)	2	2
Endometrial cancer	2	—

* Of the 740 women 126 were postmenopausal, 614 were still menstruating.

or unable to use hormone replacement therapy (HRT).

Prophylactic oophorectomy was offered to women who were postmenopausal or >45 years

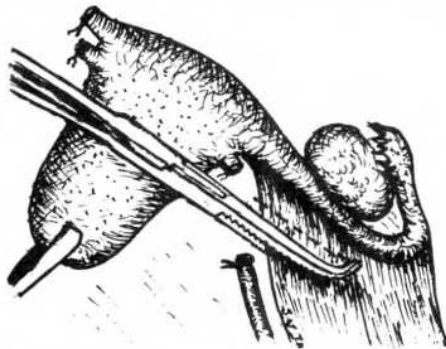


Fig. 1. The round ligament is cut and sutured separately giving free access to clamp the infundibulo pelvic ligament for salpingo-oophorectomy. The clamp is on the broad ligament and the ligated structure inferior to the clamp is the round ligament.

but still menstruating, or >40 years with a past history of ovarian neoplasm or a family history of ovarian malignancy.

Technical details

The decision to perform oophorectomy as well as salpingo-oophorectomy is reviewed after the ovarian pedicle has been cut on one side. The uterus then hinges on the contralateral ovarian pedicle. Working on the side that is still attached to the uterus, the round ligament, with the part of broad ligament inferior to it, is now cut and ligated separately to provide easy access to the infundibulo pelvic ligament (Fig. 1). If the infundibulo pelvic ligament is easily accessible and salpingo-oophorectomy appears easy, a clamp is placed above the round ligament stump to include the full length of the infundibulo pelvic ligament. One or more clamps may be necessary. A specially devised clamp (Fig. 2) with a curve of 2 cm beginning at 1 cm from the tip facilitates and accommodates the infundibulo-pelvic ligament or mesovarium efficiently. The infundibulo pelvic ligament is transfixed and

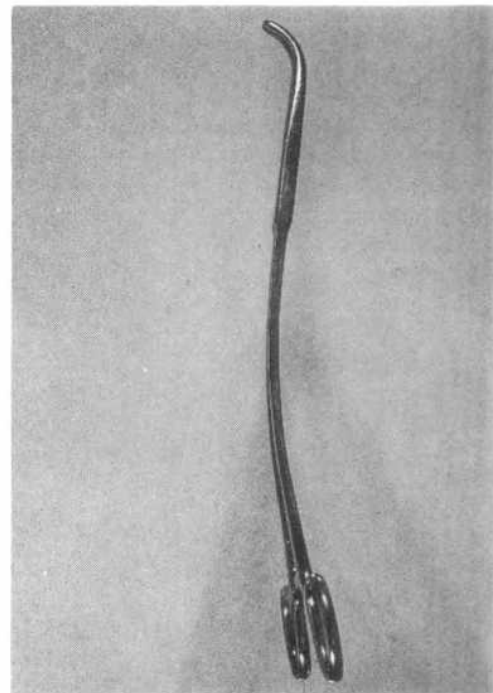


Fig. 2. A special clamp, devised by the author, for the infundibulo pelvic ligament or mesovarium with the curve beginning at 1 cm from the tip for the distance of 2 cm.

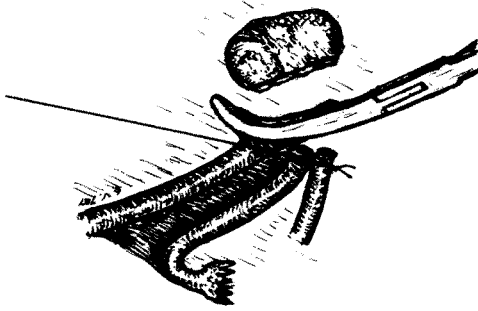


Fig. 3. Clamp on mesovarium at the time of oophorectomy.

doubly secured with a no. 1 gauge polyglactin suture (Vicryl). Attention is now turned to the remaining ovary and tube on the contralateral side where all uterine connections were severed earlier. Either salpingo-oophorectomy or only oophorectomy is performed on this remaining side.

For oophorectomy, the ovary is gently pulled into the operative field and the mesovarium is clamped to include the space between the two leaves of broad ligament, but keeping away the fallopian tube (Fig. 2). The ovary is then

removed and all pedicles are doubly ligated with no. 1 gauge polyglactin. Deaver's or Jayle's retractors are helpful. The removal of either tube depends on ease of access. After completion of the oophorectomy, the peritoneum and then the vault are closed.

Results

Prophylactic oophorectomy was possible in 702 of the 740 patients (95%), bilateral salpingo-oophorectomy in 308, unilateral salpingo-oophorectomy with contralateral oophorectomy in 180 and bilateral oophorectomy in the remaining 214 patients. It was impossible to remove one or both ovaries in the other 38 patients (5%), both ovaries in 26 patients (3%) and one ovary in 12 patients.

The following factors influenced successful oophorectomy, obesity, parity, uterine descent and size, tubo-ovarian disease and vaginal access (Table 2). Of these, tubo-ovarian disease was the most important.

In 548 operations, the extra time needed to perform an oophorectomy was 11–20 min but in 88 patients it was <10 min. In 78 patients, the additional surgery took between 21 and 30 min.

Table 2. Factors associated with failure of vaginal oophorectomy

Condition	No. of women	Oophorectomy not possible <i>n</i> (%)
Obesity		
Present	86	16 (19)
Absent	654	22 (3)
Parity		
Nulliparous	72	7 (10)
Parous	668	31 (5)
Pelvic space		
Reduced	84	18 (21)
Adequate	656	20 (3)
Patulous vagina		
Absent	312	20 (6)
Present	428	18 (4)
Uterine descent		
Absent	248	20 (8)
Third degree descent	64	0 (–)
Uterine size		
Enlarged (≤ 12 weeks)	665	36 (5)
Normal	75	2 (3)
Obese, enlarged uterus, non-patulous vagina & restricted space	56	10 (18)
Non-obese, normal size uterus, patulous vagina & adequate space	60	1 (2)

Table 3. Surgical time for vaginal hysterectomy with or without vaginal oophorectomy*

Surgical time (min)	With oophorectomy (n = 740)	Without oophorectomy (n = 700)
<30	—	98
30–45	96	258
46–60	180	240
61–90	354	88
91–120	104	16
120–150	6	—

*Vaginal hysterectomy may include anterior colporrhaphy and/or posterior colpoperineorrhaphy and/or bladder neck buttressing for stress incontinence.

The 26 patients with bilateral failure are not included here. The operating time in the group of 700 patients undergoing vaginal hysterectomy without oophorectomy was shorter (Table 3). The length of hospital stay is shown in Table 4. There was no difference in length of hospital stay between the two groups.

Complications are shown in Table 5. Blood transfusion was required in 30 patients who were anaemic before the procedure. Oophorectomy, by itself, did not necessitate blood transfusion in any patient. There were no instances of pedicle slippage. Laparotomy was not necessary in any woman and there was no injury to either ureter or bowel. There were no deaths in the two series.

In the 38 patients in whom one or both ovaries (a total of 64 ovaries) could not be removed, the causes were tubo-ovarian adhesions (n = 16), inaccessibility (n = 41) and failure to identify the ovary (n = 7).

Discussion

It is a paradox that most gynaecologists consider prophylactic oophorectomy at abdominal hys-

Table 4. Length of hospital stay in days for patients undergoing vaginal hysterectomy with or without oophorectomy

Days in hospital	With oophorectomy (n = 740)	Without oophorectomy (n = 700)
3–4	64	49
5–6	613	585
7–10	48	52
10–15	15	14
>15	0	0

terectomy but almost routinely leave the ovaries in place at vaginal hysterectomy. Studd (1989) recommended oophorectomy at the time of hysterectomy in all women over 40 years of age.

Capen *et al.* (1983) found that between 60 and 70% of ovaries could be removed per vaginam without too much difficulty and with little or no risk. Nichols (1988) has detailed the steps of oophorectomy as well as of salpingo-oophorectomy. The author has performed vaginal oophorectomy without hysterectomy to alter the hormonal milieu in women with metastatic breast cancer (Sheth 1989). In the present series, the author was able to remove both ovaries in 95% of patients at a vaginal hysterectomy and one ovary in a further 2%. The prerequisites for oophorectomy or salpingo-oophorectomy are: (i) tubo-ovarian normality; (ii) easy access to the tube and mobile ovaries with long, free infundibulo pelvic ligaments; (iii) efficient retraction and lighting; (iv) experience of vaginal surgery. Correspondingly, salpingo-oophorectomy or oophorectomy are contraindicated by adhesions, high immobile ovaries, difficulty in access and limited vaginal capacity.

Difficulties may be anticipated preoperatively and include obesity, nulliparity, decreased vaginal access and space, lack of uterine descent and increased uterine size. Intra-operative difficulties include inaccessible ovaries and tubo-ovarian disease.

Obesity can cause difficulties for the following

Table 5. Complications of surgery for patients with vaginal hysterectomy with or without oophorectomy

Complications	With oophorectomy	Without oophorectomy
Pyrexia	32	34
Urinary tract infection	224	214
Wound sepsis	9	7
Reactionary haemorrhage	7	8
Paralytic ileus	1	1
Secondary haemorrhage	0	1
Granulation tissue	40	86
Fallopian tube prolapse	24	92
Peritonitis	1	1
Resuturing of wound	0	1
Shock	10	8
Tubal tear	226	—
Blood transfusion	30	26

reasons: (i) The large vulva reduces access and may increase the distance of the ovaries from the operative field. This can be overcome by suturing the labia laterally and the mons to the lower abdominal wall. (ii) The soft tissues occupy more space in the pelvis. (iii) Increased vascularity results in more intra-operative bleeding, (iv) The tissue planes are more difficult to identify because of the fat.

Nulliparous patients have decreased vaginal laxity and uterine descent. More traction is required in these patients, and this is reflected in the higher failure rate of oophorectomy.

Space is always at a premium during vaginal surgery. Decrease in vaginal space may occur with a narrow sub-pubic arch and tense soft tissues. These may be relative contra-indications to vaginal surgery, but can be overcome in some patients with suitable traction and good illumination, such as using a separate fibre optic light source.

The essence of successful vaginal salpingo-oophorectomy lies in the separate clamping and cutting of the round ligament. This important step is not often practised and its advantages are not appreciated. Nothing is gained by leaving the fallopian tubes if they can be removed easily. A special clamp, extra gentleness, a head light and the use of long roller gauze pack facilitate the operation.

Lack of uterine descent causes occasional difficulty during hysterectomy, but does not add to the difficulty of a vaginal oophorectomy as this is performed only after the uterus has been removed.

Although a large uterus makes vaginal hysterectomy more difficult, it does not add to the difficulty of vaginal oophorectomy, since the uterus has already been removed. Intra-operative difficulties sometimes occur after completion of the vaginal hysterectomy and include unexpected tubo-ovarian disease with ovarian enlargement and adhesions between the ovary and other organs associated with past pelvic inflammatory disease or endometriosis, short infundibulo-pelvic and long ovarian ligaments leading to inaccessible ovaries. The decision as to whether to proceed must be based on the extent of the ovarian lesion and the skill of the surgeon. Adhesions may be overcome by careful blunt dissection and sharp dissection should only be performed under direct vision.

The ureter is potentially always at risk in this situation and it is important to place the ovarian

clamp as close and as medial as possible on the infundibulo pelvic ligament.

Vaginal oophorectomy in association with vaginal hysterectomy is a safe and reasonable procedure for the experienced surgeons. The most favourable factors are a slim patient, adequate vaginal space, pliable soft tissues, multiparity, uterine descent and accessory ovaries which are free from pathology. Failure in this series was due mainly to inaccessibility of ovaries associated with tubo-ovarian disease.

The surgeon planning a vaginal hysterectomy should ask himself if he would remove the ovaries if the hysterectomy was to be by the abdominal route. Experienced vaginal surgeons can achieve safe oophorectomy during vaginal hysterectomy and should adhere to the indication for this procedure that they would use if working through an abdominal wound.

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Delivery in an obstetric birth chair: a randomized controlled trial

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Abstract

Objective—To determine whether nulliparae whose second stage of labour is conducted in an obstetric birth chair have a lower incidence of instrumental delivery than those using a conventional delivery bed.

Design—Randomized controlled trial using sealed, opaque envelopes for allocation.

Setting—Delivery ward in a busy teaching hospital.

Patients—1250 nulliparae with a singleton live fetus with cephalic presentation, without epidural anaesthesia, who had achieved full dilatation.

Intervention—Intention to conduct second and third stages of labour in either the Birth-EZ chair or the conventional delivery bed, as randomly allocated.

Main outcome measures—Primary measure: vaginal operative delivery; principal secondary measures: duration of second stage, perineal trauma, blood loss, women's views, and neonatal status.

Results—Delivery in the birth chair did not result in a reduction in operative delivery, overall. However, there was a reduction in vaginal operative delivery for fetal heart rate abnormality. There was no beneficial effect on perineal trauma or puerperal perineal pain. Post-partum haemorrhage was more frequent in the birth chair group.

Conclusions—Delivery in the birth chair does not offer any obvious advantage to women over delivery on a bed.

Women giving birth in institutions in the Western world are commonly expected to adopt recumbent positions for delivery (Shorter 1984). This expectation has come under challenge over the last two decades (Roberts *et al.* 1989). Upright positions, which are common in many cultures, could improve the expulsive phase of

labour and thereby reduce the need for operative vaginal delivery and decrease perineal trauma but they could also have disadvantages, such as an increased risk of postpartum haemorrhage (Stewart *et al.* 1989). One way to facilitate an upright position is the use of a birth chair. To assess these possible benefits and hazards we mounted a large randomized trial in which delivery in a commercially available birth chair was compared with delivery on a conventional delivery bed.

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Subjects and methods

The trial was conducted at the Coombe Lying-in Hospital, Dublin between March 1984 and June 1985. Women were eligible for entry to the trial if they were nulliparae with a singleton live fetus with a cephalic presentation. All women who

Table 1. Comparability of trial groups

	Chair (<i>n</i> = 634)		Bed (<i>n</i> = 596)	
Maternal age (years) mean [SD]	24.4	[4.1]	24.3	[4.5]
No. (%) in socio-economic groups 1 to 3	236	(37.1)	176	(29.6)
No. (%) married	518	(81.7)	459	(77.3)
No. (%) induced	109	(17.2)	101	(16.9)
No. (%) accelerated	192	(30.3)	211	(35.4)
No. (%) meconium in amniotic fluid (at first inspection after admission to delivery suite)	51	(8.0)	71	(11.9)
No. (%) oxytocin in labour	294	(46.4)	307	(51.5)
No. (%) electronic fetal heart rate monitoring at any time in labour	136	(21.5)	144	(24.2)
No. (%) fetal blood sample	28	(4.4)	43	(7.2)
No. (%) pethidine	514	(81.3)	495	(83.1)
Length of first stage of labour (h)				
Mean [SD]	5.8	[3.5]	5.9	[3.5]
No. (%) <6	410	(64.7)	378	(63.4)
No. (%) >12	39	(6.2)	41	(6.9)
Birthweight (g)				
Mean [SD]	3396.2	[450]	3404.7	[456]
No. (%) <2500	15	(2.4)	13	(2.2)
Gestational age (completed weeks)				
Mean [SD]	39.7	[1.3]	39.7	[1.3]
No. (%) <37	14	(2.3)	13	(2.2)

had epidural anaesthesia or who were less than 34 weeks pregnant were excluded. This exclusion effectively excluded women with significant pre-eclampsia who were advised to avail themselves of epidural anaesthesia. Formal trial entry was delayed until full dilatation of the cervix was recorded. A numbered, sealed opaque envelope was then opened by the midwife, revealing a random allocation to either a conventional delivery bed or to the obstetric birth chair for the second and third stages of labour. Simple random allocation was generated from a table of random numbers. There was no prognostic stratification.

Ethical approval for the trial was given by the hospital research committee. Women were informed about the trial during pregnancy. They were told that the birth chair was new to the hospital and that they might be asked to participate in a trial to assess it. Those who attended antenatal classes were shown the chair during a visit to the labour ward. Formal trial entry was delayed until vaginal delivery was confidently expected to occur and consent was sought to a particular type of delivery once random allocation was known. Once told of their random allocation, those who declined to be delivered as

randomly assigned were delivered as they requested, but all analyses are based on the groups as randomly allocated.

Apart from adherence, as far as possible, to the randomly allocated policy for delivery, caregivers were free to manage the second and third stages of labour in whatever ways they felt to be appropriate. Women delivered on the bed were free to use recumbent or semi-recumbent positions in either the dorsal or left lateral position, depending on the preferences of both midwife and woman, and the position that the woman found most comfortable for pushing. For women using the Birth-EZ chair for the second and third stages of labour, the midwife conducting the delivery was free to adjust the height and angle of the chair according to her preference and that of the women.

The primary hypothesis tested in the trial was that the use of a birth chair would reduce the rate of vaginal operative delivery from the then current rate in the hospital for nulliparae of 16.6%, to 11%. A total sample size of 1300 women was planned to achieve an 80% chance of detecting a reduction of this magnitude at the 5% level of statistical significance. Other maternal outcomes considered were duration of

Table 2. Actual place of delivery

	Chair (<i>n</i> = 634)		Bed (<i>n</i> = 596)	
	No.	(%)	No.	(%)
Actual place of delivery				
Chair	413	(65)	20	(3)
Bed	221	(35)	576	(97)
Reasons for place of delivery not as randomized				
Chair unavailable	72	(11)	0	(0)
Woman refused	92	(14)	8	(1)
Doctor refused	5	(1)	0	(0)
Mother too sedated	8	(1)	0	(0)
Fetal distress	4	(1)	0	(0)
Other	29	(5)	7	(1)
Not known	11	(2)	5	(1)

the second stage of labour, occurrence of perineal trauma and of manual removal of the placenta, blood loss after delivery, and the

haemoglobin value 3 or 4 days after delivery. Neonatal effects were assessed in terms of 1 and 5-min Apgar scores, endotracheal intubation and admission to the special care nursery. During the first 8 months of the trial, an attempt was made to interview consecutive women who took part in the trial. Of the 686 women delivered over this period 331 were allocated to the chair and 355 to the bed. Completed interviews were obtained from 552 women (80%), 263 and 289 in the two groups respectively.

Statistical analysis used *t*-tests for differences in the means for continuous data, and odds ratios with 95% confidence intervals (CI) for categorical data. A multivariate analysis was used to adjust for imbalances between the trial groups. There were no interim analyses.

Results

A total of 1250 women participated in the trial.

Table 3. Maternal and neonatal outcomes of labour and delivery

	Chair (<i>n</i> = 634)		Bed (<i>n</i> = 596)		Odds ratio	95% CI
No. (%) delivery by						
Senior midwife	74	(11.7)	22	(3.7)		
Pupil midwife	450	(71.0)	418	(70.1)		
Doctor	86	(13.6)	96	(16.1)		
Medical student	24	(3.8)	60	(10.1)		
No (%) vaginal operative delivery	80	(12.6)	89	(14.9)	0.82	0.59, 1.13
No (%) reasons for operative delivery						
Failure to advance	48	(7.6)	44	(7.4)	1.02	0.61, 1.56
Fetal heart rate abnormalities	19	(3.0)	36	(6.0)	0.49	0.28, 0.84
Other	13	(2.1)	9	(1.5)	1.36	0.59, 3.16
State of perineum. No. (%)						
Intact	133	(21.0)	111	(18.6)	1.16	0.88, 1.53
Tear (no suture)	26	(4.1)	20	(3.4)	1.23	0.68, 2.22
Tear (and suture)	96	(15.2)	62	(10.4)	1.53	1.09, 2.13
Episiotomy	329	(51.9)	350	(58.7)	0.76	0.61, 0.95
Episiotomy and tear	50	(7.9)	53	(8.9)	0.88	0.59, 1.31
Mean [SD] length of 2nd stage (min)	31.7	[19.2]	31.2	[18.8]		
Mean [SD] length of 3rd stage (min)	8.2	[10.5]	8.2	[11.1]		
No. (%) manual removal of placenta	18	(2.8)	10	(1.7)	1.68	0.79, 3.55
No. (%) blood loss >500 ml	32	(5.1)	22	(3.7)	1.37	0.80, 2.37
Haemoglobin 3rd/4th postnatal day						
Mean [SD]	12.5	[1.6]	12.7	[1.6]		
No. (%) <11 g/dl	72	(11.6)	49	(8.3)	1.42	0.98, 2.07
No (%) postpartum blood transfusion	12	(1.9)	7	(1.2)	1.60	0.64, 3.95
Neonatal outcome. No. (%)						
1-min Apgar ≤5	7	(1.1)	6	(1.0)	1.09	0.37, 3.26
5-min Apgar ≤7	1	(0.2)	4	(0.7)	0.28	0.05, 1.62
Intubated	2	(0.3)	3	(0.5)	0.63	0.11, 3.63
Admitted to special care nursery	23	(3.6)	27	(4.5)	0.79	0.45, 1.39

Table 4. Results of mothers' answers to the questionnaire

	Chair (<i>n</i> = 263)		Bed (<i>n</i> = 289)	
	No.	(%)	No.	(%)
More comfortable second stage versus first	160	(61)	174	(60)
Same	30	(11)	30	(10)
Less	71	(27)	79	(27)
Don't know	2	(1)	6	(2)
Could move freely	175	(67)	195	(67)
Too restricted	79	(30)	88	(30)
Don't know	9	(3)	6	(2)
Felt in control	190	(72)	209	(76)
Felt out of control	73	(28)	80	(28)
Overall a pleasant experience	17	(6)	31	(11)
Not too unpleasant	135	(51)	131	(45)
Rather unpleasant	64	(24)	69	(24)
Very unpleasant	47	(18)	58	(20)
No perineal pain when interviewed	158	(60)	176	(61)
Mild	44	(17)	44	(15)
Moderate	45	(17)	55	(19)
Severe	16	(6)	14	(5)

There were 20 post-randomization withdrawals, of whom 7 had been allocated to the chair and 13 to the bed; 5 (2, 3) ineligible women were randomized in error and 15 (5, 10) envelopes were lost or destroyed. Our analysis is based on the remaining 1230 women, of whom 634 were allocated to the birth chair and 596 to the conventional delivery bed. The difference in the number of women in the two groups reflects the use of simple random allocation, without balancing procedures such as blocking.

Maternal characteristics of the two groups are summarized in Table 1, which indicates that the two groups were similar in a number of important respects. These characteristics apply mainly to the comparability of the two groups at trial entry, but it is possible that some of the interventions described, such as oxytocin acceleration or electronic monitoring were initiated after random allocation.

Most of the women were delivered according to their allocation, 65% of the chair group, and 97% of the bed group (Table 2). In both groups, the main reason for discrepancies was refusal by the women. In addition, a birth chair was not available for about 10% of women so allocated, either because of a short second stage or because

the delivery room containing the birth chair was already occupied.

Table 3 describes the conduct and outcome of delivery for the two trial groups. Because senior midwives found it difficult to supervise medical students performing deliveries in the birth chair, delivery by medical students was largely restricted to the conventional bed group and this was reflected in the larger numbers of deliveries by senior midwives in the birth chair group. The unusually low frequency of adverse neonatal outcomes may reflect the effect of the exclusion criteria on screening out women with more complicated labours.

Our primary hypothesis that women allocated to the chair would be less likely to have an instrumental vaginal delivery, was not sustained. Although there were somewhat fewer operative deliveries in the group allocated to the birth chair (a difference which reflected fewer forceps deliveries prompted primarily by fetal heart rate abnormalities), this difference was not statistically significant. One woman, allocated to the bed, required caesarean section for fetal distress in the second stage of labour.

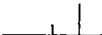
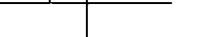
There was little difference in the overall rate of perineal trauma. In the birth chair group a lower episiotomy rate was offset by more perineal tears. Use of the birth chair had no detectable effect on the lengths of the second or third stages of labour.

Manual removal of the placenta, postpartum haemorrhage, low maternal haemoglobin and postpartum blood transfusion were all more common in the birth chair group, but none of these differences was statistically significant at the 5% level.

Neonatal outcomes appeared to be similar in the two groups (Table 3); but these 'poor' outcomes were uncommon in both groups and this is reflected in the wide confidence intervals surrounding the point estimates of the differences between the two groups.

Analysis of the mothers' answers to the questionnaires revealed striking similarities between the two groups with respect to the women's feelings of comfort during the second stage, their ability to move freely during the second stage, and the sense of being in control during the second stage (Table 4). There was no difference in the women's overall assessment of the experience of childbirth, with about 20% of women in each arm of the trial describing the birth of their babies as a 'highly unpleasant experience'.

Table 5. Effect of birth chair during second stage of labour on instrumental vaginal delivery

Study	Chair	Bed	Numerical	Odds ratios and 95% CI			
				Graphical			
				0.1	0.5	1	2
Present study (1991)	80/634	89/596	0.82 (0.59-1.14)				
Stewart <i>et al.</i> (1989)	13/157	7/147	1.77 (0.72-4.38)				
Turner <i>et al.</i> (1986)	37/318	38/318	0.97 (0.60-1.57)				
Hemminki <i>et al.</i> (1986)	17/88	8/82	2.27 (0.98-5.29)				
Stewart <i>et al.</i> (1983)	10/94	12/90	0.78 (0.32-1.88)				
Liddell <i>et al.</i> (1985)	11/27	7/21	1.38 (0.42-4.37)				
Marttula <i>et al.</i> (1983)	2/50	6/50	0.34 (0.08-1.44)				
Chen <i>et al.</i> (1987)	2/73	8/43	0.14 (0.04-0.52)				
Typical odds ratio			0.91 (0.72-1.14)				

Similarly, whether or not a woman had been allocated to be delivered in the chair or the bed did not influence the amount of perineal pain experienced in the puerperium (Table 4).

Discussion

This trial aimed to clarify the place of the birth chair for vaginal delivery in nulliparous women. The trial was confined to nulliparae, as with a vaginal operative delivery rate in parous women of only 4%, a very large trial would be required to show a reduction in this outcome. The birth chair we used is commercially available within

Britain and Ireland and is similar in many respects to alternative designs of birth chair.

The concept of using gravity to aid expulsive efforts in the second stage of labour is appealing, and as there is evidence that ambulation in the first stage of labour improves progress (Roberts 1989) there is reason to expect that delivery in the birth chair might be associated with a reduced rate of instrumental delivery. We facilitated the chances of demonstrating a useful reduction in instrumental delivery by recruiting a sufficiently large number of women to the trial and by confining the trial to nulliparae who have a higher rate of instrumental delivery than multiparae. Previously reported trials have been

Table 6. Vaginal operative delivery stratified by presence of meconium or fetal blood sample (FBS) at trial

	All		Meconium or FBS		No meconium or FBS	
	Chair (n = 634)	Bed (n = 596)	Chair (n = 65)	Bed (n = 86)	Chair (n = 569)	Bed (n = 510)
No. (%) vaginal operative delivery	80 (12.6)	89 (14.9)	15 (23.1)	16 (18.6)	65 (11.5)	73 (14.3)
No. (%) reasons for operative delivery						
Failure to advance	48 (7.6)	44 (7.4)	7 (10.9)	4 (4.7)	41 (7.2)	40 (7.9)
FHR abnormalities	19 (3.0)	36 (6.0)	2 (3.1)	10 (11.6)	17 (3.1)	26 (5.1)

Table 7. Effect of birth chair during second stage of labour on estimated blood loss >500 ml

Study	Chair	Bed	Numerical	Odds ratios and 95% CI			
				Graphical			
				0.5	1	2	10
Present study (1991)	32/634	22/598	1.38 (0.80–2.38)			—	
Stewart <i>et al.</i> (1989)	27/157	7/147	3.48 (1.71–7.10)			—	
Turner <i>et al.</i> (1986)	28/318	19/31	1.51 (0.83–2.74)			—	
Stewart <i>et al.</i> (1983)	12/94	4/90	2.84 (1.02–7.89)			—	
Typical odds ratio			1.87 (1.34–2.60)				

smaller, and have involved both nulliparous and parous women (Hemminki *et al.* 1986; Turner *et al.* 1986; Stewart *et al.* 1983; Liddell & Fisher 1985; Chan 1963). In our trial, the women recruited were at relatively high risk of sustaining perineal trauma (80%), and of operative delivery (14%).

Overall 14% of women allocated to delivery in the chair asked to be delivered in a conventional bed. The other principal reason for standard management in this group was that labour progressed too quickly to allow transfer to the delivery room with the birth chair. This is consistent with the findings in other trials (e.g., Turner *et al.* 1986). Statistical analyses are, however, based on the groups as allocated (intention-to-treat analysis) and the trial therefore compared a policy of planned delivery in a birth chair with the alternative policy of planned delivery in a conventional delivery bed.

The difference in status of the person performing the delivery reflected the fact that delivery in the birth chair was the newer, experimental policy. Senior midwives were reluctant to supervise medical students if the allocation was to the chair and tended to perform the delivery themselves.

An overview of eight randomized trials (including the one described in the present paper) of upright versus recumbent position in the second stage of labour (Table 5) showed no effect on the rate of instrumental delivery (Spiby 1990). In the Coombe Hospital trial, the results were consistent with those of other trials. However, although operative delivery in general was not reduced, delivery in the chair was associated

with a reduced rate of vaginal operative delivery for fetal heart rate abnormalities (odds ratio 0.49, 95% CI 0.28–0.84). The fewer operative deliveries prompted by fetal heart rate abnormalities may be due to chance. Alternatively, it may reflect a beneficial effect of upright posture on fetal acid-base balance or a greater ease in auscultating the fetal heart in supine women. A further possibility is that this difference may be an artefact attributable to the fact that women allocated to be delivered in the bed were already at somewhat higher risk of instrumental delivery at trial entry, as suggested by the increased rate of meconium-stained amniotic fluid and fetal blood sampling in the first stage of labour (Table 1).

A stratified analysis of results was conducted in order to examine more closely the effect of meconium or fetal blood sampling before randomization on the rate of instrumental delivery for fetal heart rate abnormalities in the second stage. Both strata show a lower rate of instrumental vaginal delivery for fetal heart rate abnormalities in women delivered in the chair, but the bulk of the difference in the overall result is attributable to the excess of instrumental deliveries in the high risk group delivered in the bed (Table 6). Multivariate analyses taking into account the potential confounders of marital status, socio-economic group and fetal heart rate monitoring as well as meconium and fetal blood sampling did not have any marked effect on our principal conclusions, the adjusted odds ratios for vaginal operative delivery were 0.82 (95% CI 0.58 to 1.16) and for intact perineum 1.23 (0.91 to 1.64). Adding the accoucheur/se to the model

changes these figures to 0.09 (0.64–1.28) and 1.17 (0.87–1.58), respectively.

Possible differences in patient characteristics at trial entry raise the question of whether midwives had broken the randomization code (by, for example, opening more than one envelope at a time) in expectation of vaginal operative delivery that is more conveniently performed in the bed. Telephone or computerized randomization would have helped to guard against such selection biases. The trial protocol might also have been violated by midwives who proceeded with randomization in circumstances which should have acted as reasons for exclusion from the trial, for instance when the chair was unavailable (Table 2). This reflected a lack of enthusiasm for the trial; this was evident among some of the staff who recognized that the trial would end when the target number of women was reached. During the trial it was apparent that such violations were taking place on a sporadic basis. Attempts to reinforce the protocol were hampered by the large numbers of midwives involved, and by the delicate professional relationships which exist between clinical midwives, research staff and obstetricians. Some obstetricians also registered a lack of approval of the birth chair by refusing to comply with the random allocation. The extent and cumulative effect of these violations is probably impossible to estimate reliably, but the possibility that an effect may exist needs to be borne in mind in interpreting the trial results.

In the absence of a reduction in instrumental delivery, use of the birth chair would still benefit women if it was associated with a lower occurrence of perineal trauma. A small reduction in the episiotomy rate was offset by an increased rate of perineal tears, a finding consistent with other randomized trials (Sleep *et al.* 1989). The likely explanation is that the perineum is less accessible during birth chair delivery and episiotomy is more difficult to perform for this reason. The reduced rate of episiotomy was of no apparent benefit to women. There was no difference in the amount of perineal pain reported by women in the two groups (Table 4).

The birth chair policy had no detectable effect on the lengths of the second and third stages of labour. Again, this is consistent with other controlled trials of birth chairs (Sleep *et al.* 1989) and runs counter to suggested benefits for upright postures for delivery.

Available data for postpartum haemorrhage

from all relevant controlled trials (including this one) are summarized in Table 7 (Spiby 1990). Taken together, they provide strong evidence that delivery in a birth chair increases the risk of post partum haemorrhage. Measurement of blood loss is potentially biased by knowledge of the trial allocation and by the practice of putting a basin under the birth chair to collect blood. In this trial, however, differences in less subjective measures of blood loss, such as haemoglobin concentration postpartum and the need for blood transfusion during the puerperium, were consistent with the difference in blood loss measured at delivery. One possible explanation is greater blood loss associated with more frequent need for manual removal of the placenta in the birth chair group. Sleep *et al.* (1989) favour the alternative hypothesis that the increased blood loss is due to bleeding from perineal trauma, exacerbated by obstruction to venous return caused by the birth chair. We observed perineal oedema and haemorrhoids in some women who used the birth chair, a finding also reported by Goodlin & Frederick (1983) and Cottrell & Shanahan (1986).

The results of the Coombe Hospital trial differ most dramatically from those of the other relevant trials with respect to women's assessment of the two positions. We were unable to detect any benefit in terms of comfort, sensation of mobility, and feelings of control during the second stage, or in terms of overall satisfaction with the birth experience. We had expected increased maternal satisfaction as previous trials had elicited more frequent positive responses from the group that had used the upright position (Sleep *et al.* 1989). It may be that in previously reported trials, women giving birth to their second baby attributed their easier delivery to using the birth chair for the first time. Enthusiastic reports in the media of the availability of the birth chair might also be expected to bias the women's outlook.

The absence of any benefit from delivery in the birth chair is disappointing, especially as there are clear benefits associated with upright posture in the first stage of labour. The small increase in blood loss at delivery may further reduce professional enthusiasm for its use. Since the completion of the trial the use of the birth chair in the Coombe Hospital has declined rapidly, and this is mainly due to an increased demand from women for epidural anaesthesia. The episiotomy rate among nulliparae delivered

spontaneously declined from 41% during the trial period to 26% in 1988. In view of the finding by Begley (1987) that the likelihood of a woman giving birth with an intact perineum was most strongly influenced by the identity of her midwife, the preference of the midwife with respect to the conduct of the second stage should not be discounted. Use of the birth chair is, of course, only one means of facilitating upright posture in the second stage.

Alternative postures such as squatting or kneeling have yet to be investigated systematically.

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Partial placenta membranacea

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Summary. Seven pregnancies complicated by partial placenta membranacea occurring over a 2-year period are described. The condition is encountered more frequently than the total or near-total form, but is similarly associated with recurrent antepartum haemorrhage, miscarriage or preterm delivery. Diagnosis by ultrasound scan may prove difficult. Five pregnancies had histological evidence of chorioamnionitis, which may have helped to precipitate labour; three fetuses showed pulmonary inflammatory changes of at least 2 days' duration. No maternal predisposing factors could be elicited.

Placenta membranacea is a rare abnormality of placentation in which restriction of villous trophoblast to the placental disc fails to develop, so that all or most of the fetal membranes remain covered by chorionic villi. This condition is associated with recurrent antepartum haemorrhage and with miscarriage in the second trimester of pregnancy. Pryse-Davies *et al* (1973), in their review of case reports, record the presence of incomplete or partial placenta membranacea. We have encountered seven examples over a 2-year period and believe that partial placenta membranacea may occur with greater frequency than the complete form; its recognition is important because it causes similar clinical problems.

Subjects and methods

All fetuses and placentas described were born at the Clarendon Wing of the Leeds General Infir-

mary. Six of the seven cases of partial placenta membranacea were recognized during autopsy of fetuses after intrauterine death or miscarriage. The seventh placenta was submitted for histological examination following the birth of a live fetus by caesarean section. The maternal histories were reviewed with particular attention to the occurrence of antepartum and postpartum haemorrhage and of placental retention. Possible predisposing factors, such as previous obstetric difficulties, non-obstetric medical problems, contraceptive usage and smoking history were also considered. The placentas and 5 of the 6 fetuses that miscarried were subjected to detailed macroscopic and microscopic examination. The sixth fetus was examined externally only before donation for anatomical dissection.

Results

Maternal complications (Table 1)

In all seven pregnancies, haemorrhage occurred in the second and/or third trimester, and, in five, there was significant loss of fresh blood. In six of the seven, the eventual outcome was intrauterine death or the miscarriage of a fresh fetus before the end of the second trimester. Placental retention occurred in two instances (nos. 2 and 6), with associated postpartum haemorrhage in one pregnancy (no. 6).

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Table 1. Maternal problems during pregnancies complicated by partial placenta membranacea

Patient	APH	Other	Delivery
1	20 and 24 wks	UTI in 1st trimester ?PROM at 20 wks	Spontaneous, vaginal. 24 wks
2	Repeated minor spotting	'Nerves' treated with oxazepam & flupenthixol	Manual removal per vaginam after failed PG infusion. 19 wks
3	14-18 wks (cont)	Offensive vaginal loss immediately before delivery	PG infusion, vaginal. 18 wks
4	17-22 wks (int)	Mildly raised AFP	Spontaneous, vaginal (membrane ruptured for 45 min). 22-23 wks
5	17 wks (minor spotting)	—	Spontaneous vaginal. 17 wks
6	16-18 wks (int)	—	Spontaneous vaginal. 17 wks
7	30 wks	—	Emergency LSCS for bleeding. 30 wks

APH = antepartum haemorrhage; wks = weeks of gestation; cont = continuous; int = intermittent; UTI = urinary tract infection; PROM = pre labour rupture of membranes; AFP = serum alpha fetoprotein concentration, PG = prostaglandin; LSCS = lower segment caesarean section.

Maternal factors possibly predisposing to partial placenta membranacea

Maternal age, gravidity, contraceptive methods and smoking habits did not appear to influence the occurrence of partial placenta membranacea, and only one of the women had used a copper-containing intrauterine device. Four women had had at least one endometrial curettage after a previous miscarriage or induced abortion or, in patient no. 7, abnormal placental retention, but such procedures are common and partial placenta membranacea is not, so that an association between them seems unlikely. Also, one of these women (no. 1) had had a normal pregnancy since the last curettage, and in the other three at least 2 years had elapsed between the last curettage and the occurrence of partial placenta membranacea.

Placental abnormalities

Table 2 summarizes the placental appearances in our study. In all pregnancies the umbilical cord was normal. Fig. 1 shows the typical appearances of partial placenta membranacea. Irregular placental tissue covers much of the surface of the gestational sac and forms only a poorly demarcated placental disc. Fig. 2 shows a section through the gestational sac in patient no. 1; a better demarcated placental disc is present, with

a thinner rim of villous tissue encroaching onto the membranes from its margin. Four of the pregnancies lacked any defined placental disc.

Acute or subacute chorioamnionitis was present in five and in three of these there were associated inflammatory changes in the fetal lungs, consisting of polymorphs in the airways together with peribronchial lymphoid aggregates. In patient no. 4, the membranous placental tissue showed focal infarction.

Ultrasound scans showed placental or uterine abnormalities in five pregnancies. Partial placenta membranacea was not specifically diagnosed, but in three instances the placenta was low-lying, or covered the internal os. In patient no. 5, a retroplacental echo-poor area was noted, and interpreted as a possible abruption. In patient no. 7 there were intrauterine adhesions, and in two patients (nos. 3 and 6) no abnormality was detected.

Fetal abnormalities

No significant abnormalities of fetal morphogenesis were found. Gestational ages ranged between 12 weeks (no. 5) and 30 weeks (no. 6). The liveborn and fresh miscarried fetuses were appropriate in size for gestational age. Two fetuses (nos. 2 and 5) showed maceration.

Six of the seven partial placenta membranacea occurred in association with male fetuses, but

Table 2. Placental appearances in seven pregnancies with partial placenta membranacea

Patient no.	U/S report of placental appearance in pregnancy	Weight (g)	Macroscopic appearances	Microscopic abnormalities
1	Overlying internal os (18 wks)	258 (with cord)	1/3 of membranes around placental disc encroached by placental tissue, 0.3 cm thick	Moderate subacute ChA
2	Placenta praevia grade I	100	2 cm wide rim of villous tissue (0.1–0.5 cm thick) around placental disc	Severe subacute ChA
3	Anterior, not low (14, 16 & 17 wks)	120	2 cm wide rim of thin villous tissue around placental disc. Green nodules on fetal surface	Moderate subacute ChA
4	Posterior, low (17 wks)	150	3/4 of membranes covered by villous tissue. No disc. Brown fetal surface	Mild subacute ChA Focal infarction of membranous placenta
5	Fundal ?anterior abruption (12 wks)	35.8	4/5 of membranes covered by thin villous tissue. No disc	Changes 2° to fetal death only
6	Posterior, not low (15–16 wks)	64	2/3 of membranes covered by thin villous tissue. No disc	Mild focal acute ChA
7	Posterior & fundal, at lower edge extending onto anterior wall with a band across uterus	420 (with cord)	Extent of villous encroachment not recorded. Entire placenta composed of 'irregular, diffuse villous tissue'	Arterial thickening in stem villi, of uncertain significance

U/S = ultrasound scan; wks = weeks of gestation; ChA = chorioamnionitis.

females are recorded in case reports (Finn 1954; Molloy *et al.* 1983; Hurley & Beischer 1987) and the significance of the present findings is doubtful.

Petechial haemorrhages were found in two fetuses, in the pericardium (no. 1) and in the skin and dura (no. 4), probably representing agonal phenomena acquired during the process of miscarriage. Inflammatory changes were seen in the lungs of three fetuses (nos. 1, 3 and 4) as described above.

Discussion

Approximately 20 cases of placenta membranacea have been reported since the term was first

used by Stein in 1807. It is rare; Janovski and Granowitz (1961) quote a frequency of 1 in 3300 placentas, but this is contrary to the experience of others (Fox 1978) and a more accurate estimate of the total or near-total form of placenta membranacea is that of 1 in 21 500 calculated by Hurley & Beischer (1987). It is an important condition because of its association with recurrent second and third trimester haemorrhage, often leading to miscarriage or preterm delivery. Intrauterine growth retardation, postpartum haemorrhage and placental retention have also been described as complications of placenta membranacea (Finn 1954; Culp *et al.* 1973; Pryse-Davies *et al.* 1973; Hurley & Beischer 1987).



Fig. 1a. Appearance of the gestational sac in patient no. 2. Intact, before fixation. Most of the surface is covered by placental tissue; the small area of fetal membranes free of placental tissue is shown at the top of the photograph, elevated by forceps. The proportion of placental to membranous tissue is much greater than normal.



Fig. 1b. Section through the same sac after formalin fixation. Thick placental tissue covers most of the gestational sac. Although placental tissue is thinner where it merges with the membranous portion of the sac (bottom of photograph), there is no demarcated placental disc.

Our seven patients showed an incomplete or partial form of placenta membranacea, with differing degrees of extension of placental tissue over the fetal membranes, and it is likely that a continuum exists between such cases and complete placenta membranacea. In eight of the cases recorded in the literature, involvement of the fetal membranes by placenta membranacea has been considered to be partial (Hertig & Shelton 1943; Culp *et al.* 1973; Pryse-Davies *et al.* 1973). We believe that partial placenta membranacea occurs more frequently than the complete form. Our seven affected pregnancies occurred over a 2-year period during which there were 8961 deliveries of livebirths, stillbirths and miscarriages at this hospital. This would give a

frequency of 1 in 1280 deliveries, which is likely to be an under-estimate as placental examination is selective rather than routine.

The clinical features in our patients are very similar to those of complete placenta membranacea. There was second or third trimester antepartum haemorrhage in all of them, the blood loss being heavy and fresh in five out of the seven. Placental retention occurred in only two instances and is known to be an inconstant feature; in the two patients reported by Finn (1954), the placenta was noted to separate easily from the uterine wall. An additional feature in five pregnancies was the presence of chorioamnionitis, with significant fetal infection before death in three. Peribronchial lymphoid aggregates occur in response to amniotic infection and denote a period of at least 48 h between intra-uterine infection and death (Emery & Dinsdale 1975). The subacute nature of the chorioamnionitic inflammatory infiltrate also indicates an infection of at least a few days standing. Chorioamnionitis has been reported previously in only two pregnancies with placenta membranacea (Pryse-Davies *et al.* 1973; Molloy *et al.* 1983) and there have been no previous descriptions of the associated lung pathology. The appearance of partial placenta membranacea is either that of a diffuse layer of cotyledons over



Fig. 2. Section through the gestational sac of patient no. 1, after formalin fixation. Placental tissue covers most of the surface, with only one sixth of the sac composed of placenta-free, membranous tissue (right side of photograph). In this case a relatively well-demarcated placental disc occupies approximately half of the sac (left side of photograph), but a rim of thinner placental tissue extends from the margin of the disc to encroach extensively on the adjacent membranous portion of the sac.

part of the gestational sac or of a placental disc with tapering placental tissue encroaching onto the membranes for variable distances from the disc margin. In the latter case, ultrasound diagnosis can only be made with difficulty, since the attenuated portion of the placenta cannot always be readily demonstrated (Pryse-Davies 1973).

The antepartum haemorrhage typical of the condition must, in many instances, be due to the abnormal location of placental tissue near or over the cervical os. However, if the attenuated placental tissue lies near the os, it may also become infected, especially if devitalized. Case reports have variously described the membranous placenta as showing focal villous degeneration (Pryse-Davies *et al.* 1973), ischaemic infarction (Molloy *et al.* 1983), and villous necrosis (Culp *et al.* 1973). Such infected placental tissue could act as a source for the amniotic fluid infection and help to precipitate early labour. In the present series, patient no. 4 showed foci of infarction within the membranous placenta.

The high mortality in our series (6 of 7) almost certainly reflects the selection of pregnancies, since placentas of live-born infants are not examined routinely. The outlook for fetal survival has been poor in the past (Fox 1978) but it is likely to improve with better survival in general of immature but normally-formed infants. We found no significant developmental anomalies in the fetuses examined, and there was no indication from the maternal histories that partial membranous placenta is a recurrent condition. We were not able to demonstrate any maternal predisposing factor. Many hypotheses have been advanced with regard to the aetiology of placenta membranacea, and are summarized by Fox (1978). One theory is that endometritis may encourage the abnormal development of villi by producing excessive endometrial vascularization, and for this reason we obtained details of the women's contraceptive methods but only one had used an intrauterine device.

Total placenta membranacea is a very rare

condition, but a partial variant occurs with greater frequency, and this diagnosis should be considered in pregnancies with recurrent second trimester antepartum haemorrhage. Abnormal location and shape of the placenta may be suggested by ultrasound scan, but diagnosis is often difficult. Chorioamnionitis may contribute to preterm labour, and the amniotic fluid infection may contribute towards subsequent neonatal morbidity.

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Autoreactivity in women with endometriosis

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Summary. Serum samples from 71 patients with laparoscopically staged endometriosis and from 109 age-matched non-pregnant control women were tested for antibodies to nuclear, phospholipid, smooth muscle and sperm antigens. Immunoglobulin G, M and A and complement components C₃ and C₄ were measured. Prevalence of the following autoantibodies was statistically significantly greater in women with endometriosis than in the control group: antinuclear antibodies, antibodies to ribonucleoproteins, smooth muscle antibodies, lupus anticoagulant and anticardiolipin antibody. Forty-one women with endometriosis (58%) had some type of autoantibody compared with 13 controls (12%). More women in the endometriosis group had IgG and IgM levels above the normal range. This was statistically significant for IgG in women with grade 3 and for IgM in those with grade 4 endometriosis, IgG levels were significantly higher in antibody-positive women with endometriosis than in the control group. Immunoglobulin and complement component levels tended to have a positive correlation with stage of disease.

The prevalence of endometriosis has been estimated to be 1-2% in the general female popula-

tion (Simpson *et al.* 1980). It is strongly associated with infertility and has been reported as occurring in up to 30% of patients undergoing laparoscopy for unexplained infertility (Insler & Lunenfeld 1986). Aetiology is still unknown but implantation of endometrial cells in ectopic locations is thought to be facilitated by a defective immune response (Dmowski *et al.* 1981). The corollary may be triggering of an auto-immune response such as that described by Mathur *et al.* (1982) towards endometrial and ovarian antigens. Abnormal autoimmune factors may be relevant either as a consequence (Steele *et al.* 1984) or a cause (Gleicher *et al.* 1987a) of the disease. The latter group presented evidence that endometriosis is characterized by polyclonal B cell activation and suggested that concomitant systemic effects may explain the infertility and fetal loss associated with endometriosis. Reduced in vitro fertilization rates per oocyte have been reported in patients with endo-

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metriosis (El-Roeiy *et al.* 1987), although this may be due to a functional defect of the oocyte leading to ovulatory disorder rather than to autoimmune factors (Wardle *et al.* 1985). We have attempted a further assessment of the significance of autoreactivity in endometriosis by testing patients for autoantibodies to nuclear, phospholipid and smooth muscle antigens.

Patients and methods

Serum samples were obtained from 71 patients with laparoscopically confirmed endometriosis. The condition was classified into Stage 1, 2, 3 or 4 endometriosis (Buttram 1985). Thirty patients had grade 1 (42%), 24 grade 2 (34%), 14 grade 3 (20%) and 3 grade 4 (4%) disease. Thirty-seven patients were nulliparous and 31 were parous (3 not known). Six women had received danazol at some time before collection of sera and five further women were taking danazol at the time that blood was obtained. Endometriosis was diagnosed in 49 women at the time of either laparoscopy, laparotomy or hysterectomy for pelvic pain (30), deep dyspareunia (3), dysmenorrhoea (2), pelvic mass (5), ovarian cyst (3) and fibroids (6). Seventeen women were asymptomatic, presenting with infertility, and in five other women endometriosis was an incidental finding at laparoscopic sterilization. In addition serum was studied from 109 normal non-pregnant women aged between 20 and 40 years (mean 31.6 years). The mean age of the women with endometriosis was 33.5 years (range 16–50 years).

Serum samples were stored at -70°C and antibodies to nuclear antigens and soluble ribonucleoproteins were assayed by immuno-

fluorescence, counterimmunoelectrophoresis, double immunodiffusion and Western blots as described previously (Taylor *et al.* 1988). Lupus anticoagulant was detected by prolongation of the activated partial thromboplastin time (Tate & Scott 1984) and anticardiolipin antibodies were measured using an enzyme immunosorbent assay validated by an international workshop (Harris *et al.* 1987). Levels of anticardiolipin antibody were defined using GPL and MPL units for IgG and IgM respectively, these being the equivalent to the cardiolipin binding activity of $1\text{ }\mu\text{g/ml}$ of an affinity purified IgG/IgM anticardiolipin antibody from a standard serum. Smooth muscle IgG, IgM and IgA antibodies were detected using indirect immunofluorescence on rodent substrates. Serum immunoglobulin G, M and A and complement components C_3 and C_4 levels were determined by standard radial immunodiffusion techniques. Antisperm antibodies were detected with an enzyme immunosorbent assay using whole sperm as the antigen. We could not perform all the tests for autoantibodies in every woman because of limited volume of serum available. There was no selection for this.

Results were analysed by Student's *t*-test or the χ^2 distribution, as indicated in the text.

Results

Serological findings in relation to autoantibodies tested for are shown in Table 1. Prevalence of all the following autoantibodies was statistically significantly elevated in women with endometriosis compared with the control group (χ^2 -test); antinuclear antibodies detected by immunofluorescence on both rodent and Hep-2 substrates;

Table 1. Distribution of positive antibodies

Antibody	Endometriosis	Control (<i>n</i> = 109) <i>n</i> (%)	Significance <i>P</i> (χ^2 -test)
	No. positive/ No. tested (%)		
Antinuclear	19/68 (27.8)	5 (4.6)	<0.001
Anti-Hep 2	19/40 (47.5)	7 (6.4)	<0.001
Anti-Ro (SS-A)	2/71 (2.8)	1 (0.9)	<0.01
Anti-La (SS-B)	2/71 (2.8)	1 (0.9)	<0.01
Anti-smooth muscle	25*/69 (36.2)	5* (4.6)	<0.001
Lupus anticoagulant	2/46 (4.3)	0	<0.05
Anticardiolipin	7†/71 (9.9)	0	<0.001

* all IgG.

† 2 IgG; 2 IgM, 3 both.

Table 2. Levels of immunoglobulin GM and A and complement components C₃ and C₄ in patients with endometriosis and normal controls

Patient group	n	IgG (mg/dl)	IgM (mg/dl)	IgA (mg/dl)	C ₃ (mg/dl)	C ₄ (mg/dl)
Normal control	109	1188 (2.8)	269.4 (117)	236.2 (85.3)	82.1 (18.7)	24.1 (8.4)
Endometriosis						
Total group	71	1252 (314)	265.8 (105)	226.6 (77.3)	82.1 (24.1)	26.8 (10.1)
Grade 1	30	1288 (291)	246.1 (108)	225.8 (79.0)	83.0 (28.3)	24.1 (11.3)
Grade 2	24	1213 (280)	270.7 (93.9)	224.5 (82.0)	77.0 (19.5)	25.4 (8.0)
Grade 3	14	1203 (398)	282.1 (121.5)	212.0 (51.9)	84.9 (20.1)	25.9 (5.9)
Grade 4	3	1443 (432)	348.3 (49.2)†	321.7 (91.7)	101.9 (28.6)	37.7 (14.3)
Antibody positive	41	1299 (316)*	287.8 (103)	241.4 (76.3)	80.1 (19.2)	25.2 (6.6)

Results are means (SD) values

* Compared with normal control group $P < 0.05$ (*t*-test)

† Compared with grade 1 patients $P < 0.05$ (*t*-test).

antibodies to the ribonucleoprotein antigens Ro and La; smooth muscle antibodies; lupus anticoagulant and anticardiolipin antibody. The total number of women with endometriosis having some type of autoantibody was 41 of 71 (58%) compared with 13 of 109 control women (12%). The smooth muscle antibodies in both the endometriosis group and the normal controls were of low titre, up to 1 in 20. Of the five patients with IgG anticardiolipin antibodies detected in the endometriosis group, three had low positive (5.2–15 GPL), one medium positive (15–80 GPL) and one strong positive (>80 GPL) antibody. Four of the five patients with IgM anticardiolipin antibodies detected had low positive and one strong positive antibody. When autoantibody prevalences were analysed by grade of endometriosis, there was a tendency for positivity of antinuclear antibodies to rise and anticardiolipin antibodies to decrease with increasing grade, the difference between grade 1 and grade 4 patients with respect to antinuclear antibodies was statistically significant ($P < 0.05$; χ^2 test).

Immunoglobulin and complement component levels are shown in Table 2. There was no significant difference in any of these factors between the women with endometriosis and the normal controls although both IgG and C₄ levels were higher in patients with endometriosis. The proportion of subjects with IgG and IgM levels above the normal range was higher in the endometriosis group than in the controls and this was statistically significant for IgG in grade 3 patients ($P < 0.01$) and IgM in grade 4 patients ($P < 0.05$, χ^2 -test). Table 2 also shows immunoglobulin and complement component levels in patients with

endometriosis who had at least one type of autoantibody. The increased levels of IgG, IgM and IgA in the endometriosis group were significant for IgG ($P < 0.05$, *t*-test). There was a tendency for a positive correlation between the stage of the disease and levels of immunoglobulin and complement components and this was significant for IgM ($P < 0.05$, *t*-test), between grade 1 and grade 4 patients. Four of the patients with endometriosis and one in the control group had IgG antisperm antibodies.

Discussion

These results indicate a high level of autoreactivity in women with endometriosis. The increased prevalence across a range of antibodies lends support to previous evidence for both organ-specific (Mathur *et al.* 1982) and non organ-specific (Gleicher *et al.* 1987a) immune responses.

In recent years, an immune component has been recognized in several types of reproductive failure at various levels including fertilization, implantation and the development of the fetoplacental unit. There is evidence that in some women various types of abnormal gestation are characterized by particular autoantibody profiles (Taylor *et al.* 1986). Antiphospholipid antibodies (Harris *et al.* 1986) and antibodies to ribonucleoproteins (Maddison *et al.* 1984) have been correlated with fetal loss. Women suffering from unexplained infertility have been shown to have elevated levels of autoantibodies to smooth muscle and phospholipid antigens (Gleicher *et al.* 1987b; Taylor *et al.* 1989). It is of interest that pregnancy loss associated with endometriosis is

reported to be more frequent in stage 1 patients (Wheeler *et al.* 1983). Prevalences of antiphospholipid antibody were found to be higher, in our study and that of Gleicher *et al.* (1987a), in such stage 1 patients. Autoantibody effects may underlie the association between endometriosis and infertility; 11 patients in our study presented with primary and six with secondary infertility.

Alterations in detection of autoantibodies may occur in relation to treatment. Of six women who had received danazol at some time previous to collection of sera, two had anticardiolipin antibody and anti-Ro (SS-A)/La (SS-B) antibodies and four had no detectable antibodies. Five other patients were receiving danazol therapy at the time of testing; none had anticardiolipin or antinuclear antibodies but four had anti-smooth muscle antibodies. In addition to exerting endocrine effects through receptor binding, danazol is thought to have immunosuppressive properties. It has been reported to decrease IgG antiphospholipid antibodies significantly in patients with endometriosis (El-Roeiy *et al.* 1988). Clarification of the effects of danazol on individual antibodies and correlation with suppression of disease will clearly be of interest in confirming the clinical importance of this treatment and in providing information about autoantibody pathogenicity.

The detection of a variety of autoantibodies in patients with endometriosis is compatible with a state of polyclonal B cell activation, often characterized by increased total immunoglobulins. These have been reported as both unchanged (Mathur *et al.* 1982; El-Roeiy *et al.* 1988) and decreased (Meek *et al.* 1988), whereas Gleicher *et al.* (1987a) found an increase in IgG levels in endometriosis patients, and in IgG and IgA levels in lupus anticoagulant-positive patients compared with those who were lupus anticoagulant-negative. In our study IgG levels were significantly higher in women with endometriosis who had at least one type of autoantibody. These findings and the positive correlation between stage of disease and immunoglobulin levels, also previously noted by El-Roeiy *et al.* (1988), support a role for autoimmune processes in endometriosis although a concomitant increase in level of autoantibodies was observed in the present study only with respect to those directed towards nuclear antigens; antiphospholipid antibodies tended to decrease with increasing grade.

Differences in complement component levels

between patients with endometriosis and normal women might be expected, either a depression due to hypercatabolism in the formation of immune complexes or an elevation as a consequence of increased synthesis during an inflammatory process. Decreased levels of C₃ and C₄ were found by Meek *et al.* (1988), substantiating previous findings of complement component deposition on the epithelial cells of endometrial glands of a patient with endometriosis (Weed & Arquembourg 1980). Badaway *et al.* (1984) reported increased concentrations of C₃ and C₄ in the serum and peritoneal fluid of patients with endometriosis. In our study there was a positive correlation between stage of disease and levels of C₃ and C₄, although differences between the grades did not attain statistical significance. Due to the broad normal range of complement concentrations serial measurements in individuals with endometriosis may be required to determine whether these levels can be utilised as an index of disease activity.

It has been suggested that endometriosis fulfils the classic characteristics of an autoimmune disease (Gleicher *et al.* 1987a). Our findings support the concept of a high level of autoreactivity in endometriosis, although it is clear that some women with this disease do not exhibit signs of a polyclonal B cell activation. Furthermore, a causal role of autoantibody in producing disease or interfering with the reproductive process remains undefined.

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Maternal plasma corticotrophin-releasing hormone— elevated in preterm labour but unaffected by indomethacin or nylidrin

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Summary. The role of corticotrophin-releasing hormone (CRH) in preterm labour was studied in 23 women in preterm labour at between 26 and 33 weeks gestation who were randomly allocated to receive treatment with indomethacin ($n=11$) or with nylidrin a beta-sympathomimetic agent ($n=12$). Maternal plasma CRH in the preterm group (median 70, range 9–597 pmol/l) before therapy was higher ($P<0.05$) than that in 23 control pregnancies, without uterine contractions, matched for gestational age (median 51, range 4–127 pmol/l). CRH levels determined after 3 and 24 h of treatment showed a 10% decrease in the indomethacin group and 10–20% decrease in the nylidrin group, but these changes were not statistically significant. After cessation of uterine contractions during tocolysis, 12 women proceeded to give birth preterm (<37 weeks) and their pretreatment CRH levels (median 195, range 9–597 pmol/l) were higher ($P<0.05$) than those in women whose pregnancy proceeded to term (median 52, range 16–207 pmol/l). In another group of women, full-term labour was not accompanied by any changes in maternal CRH levels. Umbilical plasma CRH levels were 1.1–9.8% of the paired maternal levels and did not rise with advancing gestational age. Nor had the type of delivery (elective caesarean section before labour, or preterm or term vaginal delivery) any effect on fetal CRH levels. Neither maternal nor fetal CRH was related to maternal or fetal cortisol levels. We conclude that: (i) maternal CRH is elevated in preterm labour, (ii) maternal CRH is not affected by treatment with indomethacin or nylidrin and (iii) fetal CRH is of no significance in the initiation of preterm or term labour.

Corticotrophin-releasing hormone (CRH), originally isolated from the ovine hypothalamus by

Vale *et al.* (1981), stimulated the synthesis of ACTH in various *in vitro* models (Shibasaki *et*

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al. 1982; Saijonmaa *et al.* 1988; Robinson *et al.* 1988). During pregnancy, the placenta becomes the most significant source of CRH, and accounts for an approximately 50-fold rise in CRH levels in maternal plasma during the last trimester of pregnancy (Shibasaki *et al.* 1982; Saijonmaa *et al.* 1988; Robinson *et al.* 1988; Sasaki *et al.* 1984; Goland *et al.* 1986; Campbell *et al.* 1987; Laatikainen *et al.* 1987; Wolfe *et al.* 1988a). Other sources of CRH may include the amnion and decidua both of which are capable of producing CRH *in vitro* (Jones *et al.* 1989). CRH is also present in fetal blood, where concentrations are approximately 1–10% of the respective maternal levels (Economides *et al.* 1987) and it has been detected in the amniotic fluid (Laatikainen *et al.* 1988).

The significance of the hypothalamic-pituitary-adrenal axis in the initiation of preterm or term labour has been studied thoroughly (Casey & MacDonald 1988; Challis 1989). Briefly, the rise of fetal ACTH triggers labour in sheep, but not in women. Nevertheless, the intactness of the fetal hypothalamic-pituitary axis may be a factor in human labour, as suggested by the incorrect timing of labour in women whose fetuses have structural abnormalities of the hypothalamic-pituitary-system; both preterm and post-term birth are common (Casey & MacDonald 1988; Challis 1989). Also, cortisol levels increase both in maternal and fetal blood in response to labour (Casey & MacDonald 1988; Challis 1989).

CRH could be a factor in the initiation of labour through an effect on the pituitary-adrenal axis or by otherwise promoting fetal maturity (Robinson *et al.* 1988; Laatikainen *et al.* 1988). The labour-promoting effect of CRH could be mediated through oxytocin and prostaglandins (Liggins & Wilson 1989), since an oxytocin-induced rise in placental synthesis of CRH (Petraglia *et al.* 1987) could potentiate the effect of oxytocin on the contractility of the myometrium (Quarero & Fry 1989). Supporting the role of CRH in labour are data on increasing CRH concentrations in maternal plasma during term labour (Campbell *et al.* 1987; Stalla *et al.* 1989), although these findings have been disputed (Goland *et al.* 1986; Laatikainen *et al.* 1987). In addition to prostaglandins (Jones & Challis 1989), mediators such as noradrenaline and adrenaline also stimulate placental synthesis of CRH *in vitro* (Petraglia *et al.* 1989). We have investigated maternal and umbilical plasma con-

centrations of CRH and cortisol in women in preterm labour randomly assigned to receive tocolytic treatment with a prostaglandin synthesis inhibitor, indomethacin, or a beta-sympathomimetic agent, nylidrin.

Subjects and methods

The study included 89 pregnant women in five different categories (Table 1). The study was approved by the local ethics committee. All the women received both written and oral information about the study and all of them gave informed consent.

One group comprised 23 otherwise healthy women with singleton pregnancies who were admitted to the hospital because they appeared to be in preterm labour at between 26 and 33 gestational weeks. They all had regular painful uterine contractions at <10-min intervals, and the cervix was softened and open (the median Bishop score was 6 (range 2–8) (Bishop 1964). The fetal membranes were intact. As the control group we studied 23 healthy pregnant women without uterine contractions who were matched for gestational age.

The other groups included 43 women at term. Of these 12 were studied 12–24 h before the onset of labour contractions, and 11 were studied after being in labour for 3–12 h (the cervix was open 5–10 cm dilated). The last group comprised 20 women who were delivered at term of healthy infants by elective caesarean section under epidural anaesthesia (narrow pelvis, previous caesarean section). The clinical characteristics of the study population are given in Table 1.

Tocolytic therapy

The 23 women who appeared to be in preterm labour were assigned in random order (using sealed envelopes) to receive treatment either with indomethacin (11 women) or nylidrin (12 women). The two groups were similar for maternal age, gestation and distribution of parity.

The indomethacin (Orion Pharmaceutica, Finland) course lasted 3 days and consisted of an initial 100 mg rectal suppository followed by two 50 mg oral capsules at 8-h intervals for the first day; on days 2 and 3 the dose was 50 mg given orally, three times a day.

Nylidrin (buphenine hydrochloride, Orion

Table 1. Clinical characteristics of the study population

	Preterm pregnancy		Term pregnancy		
	Preterm contractions (n=23)	No contractions (n=23)	Before labour (n=12)	In labour (n=11)	Elective caesarean section (n=20)
Age (years)					
Median	29	29	30	32	30
Range	(22-39)	(22-38)	(22-38)	(21-39)	(22-39)
Gestational age (weeks)					
At study					
Median	28	28	40	40	39
Range	(26-33)	(26-33)	(38-41)	(37-41)	(37-40)
At delivery					
Median	36	40	40	40	39
Range	(26-41)	(37-41)	(38-41)	(37-42)	(37-40)
	$P<0.05$				
Birthweight (g)					
Median	2575	3620	3435	3990	3350
Range	(680-3890)	(2860-4160)	(2830-4000)	(3160-4370)	(2680-4250)
	$P<0.05$				

Pharmaceutica, Finland) was infused intravenously at an initial dose of 50 µg/min, this was increased within 30 min to the maximum of 150 µg/min. The nylidrin infusion was continued for 3 days. The principle of double-dummy technique was followed so that all patients received the intravenous infusion (containing nylidrin or placebo) or rectal suppositories and oral capsules (containing indomethacin or placebo).

Blood sampling

Venous blood samples from the women were collected in ice-cold test tubes containing EDTA as an anticoagulant. In women with preterm labour the sampling took place at admission, before tocolytic treatment, and was repeated 3 and 24 h later, during treatment. In the 20 women delivered by elective section maternal blood samples for CRH were collected before the insertion of either the intravenous or the epidural cannula.

A mixed blood sample was collected from the umbilical cord immediately after the birth of 23 infants born vaginally (12 preterm and 11 at term), whereas separate samples were obtained from both the umbilical artery and vein immediately after birth in the 20 infants born by elective caesarean section.

Plasma was separated at 4°C by centrifugation

at 1500 g for 10 min. and stored frozen at -21°C. CRH was estimated by radioimmunoassay as described by Laatikainen *et al.* (1987). Briefly: 50-200 µl of plasma was diluted with 2 ml of 20% acetonitrile in 0.1 N HCl, and the mixture was put through Sep Pak C 18 cartridges (Water Associates Inc., Milford, MA, USA), activated with 5 ml of methanol, 10 ml of distilled water and 5 ml of 20% acetonitrile in 0.1 N HCl before use. After application of the sample, the cartridges were washed with 10 ml of 20% acetonitrile in 0.1 N HCl, and CRH was eluted with 4 ml of 60% acetonitrile in 0.1 N HCl. The mean recovery of CRH added to plasma samples was 62%, and no correction for losses was made. The intra- and interassay variations of CRH determinations were 6.8% and 11.0%. Plasma cortisol was measured using a commercial RIA kit (Farnos Diagnostica, Turku, Finland). The intra- and interassay variations were 2.8% and 5.0%.

Statistical analyses involved Spearman's correlation, Student's *t*-test for unpaired and paired observations (umbilical vein and artery blood) and the Wilcoxon signed rank test. To improve the detection of any possible treatment-induced changes, CRH and cortisol values during indomethacin and nylidrin therapy were also expressed as a percentage of the woman's initial level.

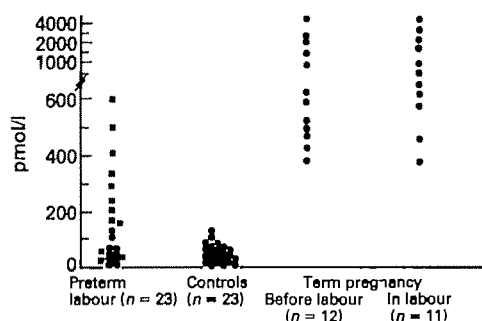


Fig. 1. Plasma corticotrophin releasing hormone (CRH) levels in four groups of pregnancies: (1) 23 in preterm labour; (2) 23 controls matched for gestational age; (3) 12 before labour at term; (4) 11 in labour at term.

23 women in group 1, 12 were delivered preterm (■) and 11 at term (●). CRH levels were significantly higher ($P<0.05$) in the preterm labour group than in the control group.

Results

Effects of tocolytic treatment

The treatment lasted 3 days in 11 women receiving indomethacin and in nine women receiving nylidrin. In the other three women in the nylidrin group, uterine contractions stopped after 24–48 h treatment and treatment was discontinued. Labour was halted for more than 24 h in all 23 women in preterm labour, and was postponed beyond the 37th week in 11 women; seven of them (64%) received indomethacin and four (36%) nylidrin. Twelve women were delivered before the 37th week (median 33, range 26–36 weeks); four of them (33%) received indo-

methacin and eight (68%) nylidrin. The median birthweight of the preterm infants was 1995 g (range 680–2610).

Plasma CRH concentrations

The women in preterm labour had higher CRH concentrations at admission (median 70, range 9–597 pmol/l) ($P<0.05$) than those in the gestational age-matched control group who had no uterine contractions (median 51, range 4–127 pmol/l) (Fig. 1, Table 2). Within the subgroups with preterm labour, CRH concentrations in women who, after cessation of contractions during tocolysis, were delivered preterm (median 195, range 9–597 pmol/l) were higher ($P<0.05$) than that in women who proceeded to delivery at term (median 52, range 16–207 pmol/l) (Fig. 1).

In the 23 women studied at term there was no difference in CRH levels between those sampled just before labour and those sampled in labour although labour was associated with a rise in cortisol levels (Fig. 1, Table 2).

Pretreatment CRH levels did not differ significantly between the groups treated with indomethacin (median 52, range 9–356 pmol/l) and nylidrin (median 166 range 28–597 pmol/l). Indomethacin treatment was accompanied by a fall of about 10% in CRH levels at 3 and 24 h and that of nylidrin by a fall of 10–20% at parallel times; but these changes were not significant (Fig. 2). Cortisol levels fell significantly ($P<0.05$) 3 h after the start of therapy in both treatment group (Fig. 2).

The CRH level in umbilical blood was not

Table 2. Maternal plasma concentrations of corticotrophin-releasing hormone (CRH) and cortisol in the study population

Preterm pregnancy			Term pregnancy		
	Preterm contractions (n=23)	No contractions (n=23)	Before labour (n=12)	In labour (n=11)	Elective caesarean section (n=20)
CRH (pmol/l)					
Median	70	51	1137	1156	1107
Range	(9-597)	(4-127)	(368-4100)	(350-4014)	(358-4001)
	<i>P</i> <0.05				
Cortisol (nmol/l)					
Median	519	534	526	764	547
Range	(206-1268)	(345-827)	(393-899)	(413-1099)	(466-890)
			<i>P</i> <0.05		

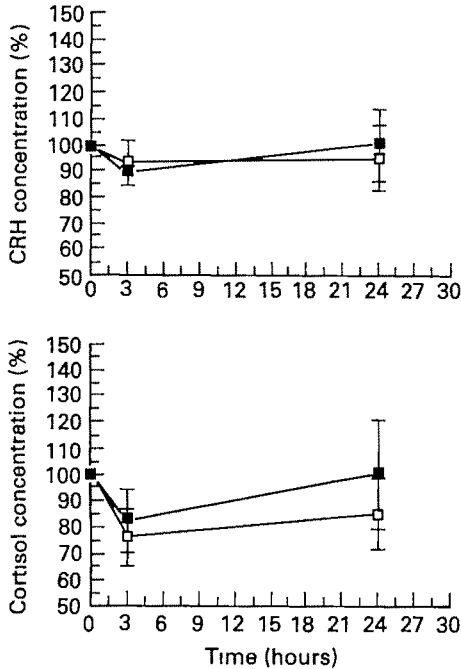


Fig. 2. Maternal plasma concentrations (mean $\pm$ SE) of corticotrophin-releasing hormone (CRH) and cortisol expressed as a percentage of pretreatment levels in women in preterm labour during treatment with indomethacin ($\square$) or nylidrin ($\blacksquare$). The decrease in cortisol was significant ($P < 0.05$) in both treatment groups at 3 h.

dependent on the mode of delivery whereas active labour, either at term or preterm, was accompanied by a rise in umbilical cortisol (Table 3). CRH levels in umbilical plasma were only 1.1–9.8% of the respective maternal levels in 43 infant-mother pairs. CRH levels ($n=20$) in the umbilical artery (median 7, range 2–18 pmol/l) or vein (median 12, range 2–22 pmol/l)

did not differ significantly, as tested by the paired t -test.

No significant correlation existed between maternal CRH and maternal cortisol ($r=0.30$; $n=43$; $P=0.180$) or between fetal CRH and fetal cortisol ($r=0.10$; $n=43$; $P=0.915$). Maternal CRH, as studied 12–24 h before or during labour at term correlated with the fetal umbilical CRH ($r=0.60$; $n=11$; $P < 0.05$), but no correlation was observed between maternal cortisol and fetal cortisol ($r=0.30$; $n=11$; $P=0.450$), or between placental weight and maternal CRH levels ($r=0.15$; $n=31$; $P=0.710$).

Discussion

It is well established that CRH levels in maternal plasma rise approximately 10–50 fold during the last trimester of pregnancy (Sasaki *et al.* 1984; Goland *et al.* 1986; Campbell *et al.* 1987; Laatikainen *et al.* 1987; Wolfe *et al.* 1988a). This finding was confirmed in the present study; the CRH concentration rose approximately 20-fold from a median of 51 pmol/l at 28 gestational weeks to a median of 1137 pmol/l before the onset of term labour. There is also a general consensus that the rise in maternal CRH during the last trimester of pregnancy originates mainly from the placenta (Shibasaki *et al.* 1982; Saijonmaa *et al.* 1988; Robinson *et al.* 1988; Sasaki *et al.* 1984; Goland *et al.* 1986; Campbell *et al.* 1987; Laatikainen *et al.* 1987; Wolfe *et al.* 1988a); other sources could include the decidua or amnion, which also produce CRH (Saijonmaa *et al.* 1988; Jones *et al.* 1989).

Preterm uterine contractions were associated with elevated maternal plasma CRH concentrations whereas term labour was not associated with any further elevation in maternal plasma

Table 3. Umbilical plasma concentrations of corticotrophin-releasing hormone (CRH) and cortisol in preterm (<37 weeks gestation) and term infants born vaginally or by caesarean section

	Preterm labour Mixed blood	Term labour Mixed blood	Elective caesarean section at term Vein blood	Artery blood
No. of infants	12	11	20	20
CRH (pmol/l)				
Median	11	13	12	7
Range	(4–33)	(2–26)	(2–22)	(2–18)
Cortisol (nmol/l)				
Median	379 ^a	333 ^b	157 ^c	not done
Range	(86–1113)	(159–602)	(83–366)	

a and b compared with c. $P < 0.05$ Wilcoxon test.

CRH. We may thus conclude that maternal stress probably does not account for the rise in CRH associated with preterm labour. This increase probably originates from the immature placenta and/or decidua, which may have the capacity to react to uterine contractions by an increased output of CRH. Our data do not allow us to deduce whether this phenomenon is solely a result of increased release of CRH due to placental 'compression' or whether the synthesis of CRH is actually stimulated. The latter explanation is supported by our finding that the rise in CRH was more marked in women who were subsequently delivered preterm than in those who gave birth at term although we found no difference in the degree of uterine activity between these two subgroups. The mechanism could include prostaglandins being increasingly produced and released during preterm labour (Liggins & Wilson 1989) and this may stimulate CRH synthesis in the placenta (Petraglia *et al.* 1987) and fetal membranes (Jones & Challis 1989). Our data on increased CRH levels in women with subsequent preterm delivery accord with Wolfe *et al.* (1988b) who found an elevation in maternal CRH in 4 of 5 women several weeks before the onset of preterm labour.

In view of the data that prostaglandins (Petraglia *et al.* 1987; Jones & Challis 1989) and sympathomimetic amines (Petraglia *et al.* 1989) may stimulate CRH synthesis *in vitro*, our finding of no change in CRH levels following the prostaglandin-synthesis-inhibitor indomethacin and the beta-sympathomimetic nylidrin are of interest. Theoretically, the rather large dose of indomethacin that inhibit uterine contractility through a fall in prostaglandin synthesis (Keirse *et al.* 1989) should have decreased, and nylidrin should have increased CRH levels, but we found that both indomethacin and nylidrin were associated with a slight, although not significant, decrease in CRH levels. This was perhaps a consequence of the inhibition of uterine contractions rather than a direct effect on CRH synthesis. Our data thus suggest that prostaglandin synthesis inhibitors or beta-sympathomimetics have no, or minimal, effect on placental CRH synthesis *in vivo*.

In accordance with previous data (Sasaki *et al.* 1984; Goland *et al.* 1986; Wolfe *et al.* 1988a; Economides *et al.* 1987), umbilical CRH levels were correlated with the respective maternal values but were only about 1–10% of maternal levels. This suggests that CRH is released into

maternal and fetal blood from the same source, probably from the placenta (Shibasaki *et al.* 1982; Saijonmaa *et al.* 1988; Robinson *et al.* 1988; Sasaki *et al.* 1984; Wolfe *et al.* 1988a), although in the present study, no statistically significant relation between maternal CRH levels and placental weight emerged. Furthermore, no significant difference was seen in CRH levels between umbilical vein and artery. This agrees with data reported by Campbell *et al.* (1987), but disagrees with those of others (Goland *et al.* 1986; Sasaki *et al.* 1987) who reported higher CRH levels in umbilical vein than in artery. As a new finding, we report that umbilical CRH levels did not rise with advancing gestational age, and were not affected by the presence of uterine activity, whether preterm or term. Thus it is unlikely that fetal CRH is of significance for the initiation of human labour. CRH levels in umbilical plasma at or near term in our study were approximately 1–10% of the respective maternal levels, which fits with the data from the second trimester (Economides *et al.* 1987). This also implies that fetal CRH synthesis does not change dramatically with advancing gestation.

Cortisol levels in maternal and fetal blood in our study accord with previous data (Casey & MacDonald 1988). These levels did not relate to the concentration of CRH and this is in accordance with previous data (Sasaki *et al.* 1984; Goland *et al.* 1986; Economides *et al.* 1987; Wolfe *et al.* 1988a). Thus, it is likely that CRH does not have a role in control of the function of the pituitary-adrenal axis in pregnancy. Evidently, any excess of CRH in maternal blood is bound to a specific binding-protein that may limit its biological activity (Linton & Lowry 1986; Orth & Mount 1987).

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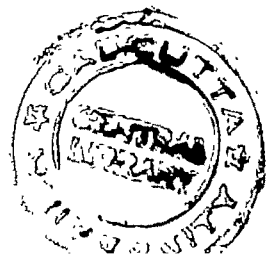
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Prediction of lethal pulmonary hypoplasia and chorioamnionitis by assessment of fetal breathing

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Summary. Twenty-three pregnancies with fetuses at risk for pulmonary hypoplasia were studied weekly until delivery. The amount of time spent in fetal breathing activity was recorded under controlled conditions during 1 h using real-time ultrasound. An amniotic fluid index was determined. The clinicians and the pathologist were unaware of the ultrasound findings. Eight of 23 fetuses did not breathe at the last ultrasound examination. Three babies died of pulmonary hypoplasia and two of these showed fetal breathing before birth. The three deaths were associated with rupture of the membranes at ≤ 20 weeks gestation and of ≥ 44 days duration. One infant developed bronchopulmonary dysplasia. The amniotic fluid index in these four pregnancies was low and the newborn infants had limb contractures. Chorioamnionitis/funisitis was noted in 13 placentas. Eight fetuses were assessed for fetal breathing within 2 days of birth. The lack of fetal breathing had sensitivity, specificity, positive and negative predictive values of 0.75 for chorioamnionitis/funisitis. In this pilot study the absence of fetal breathing was of no value in predicting lethal pulmonary hypoplasia, but was related to chorioamnionitis/funisitis. We recommend further studies of fetal breathing in relation to fetal/neonatal infections.

It is controversial whether the absence of fetal

breathing (FB) can predict lethal pulmonary hypoplasia (Fox & Moessinger, 1985; Blott *et al.*, 1987; Moessinger *et al.* 1987; Greenough *et al.* 1988, Blott & Greenough, 1988). A significant correlation between absence of FB and presence of bacteria in amniotic fluid has been reported (Goldstein *et al.* 1988) and the lack of FB movements has also been associated with amnionitis and neonatal infection (Kivikoski *et al.* 1988). In a retrospective unblinded study, in which the test results were known to the attending physicians, the presence of FB activity was suggested to be a good predictor of an outcome free of infection (Vintzileos *et al.* 1986).

This blind prospective pilot study was designed to determine if ultrasound assessment of FB movements is of value in the prediction of pulmonary hypoplasia and/or chorioamnionitis/funisitis. The study was approved by the

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Research Ethics Board of the Women's College Hospital.

Subjects and methods

After informed consent, 23 women with singleton pregnancies and fetuses at risk for lung hypoplasia because of preterm prelabour rupture of the membranes (PROM) at ≤ 30 weeks gestation were enrolled in the study between February 1988 and January 1989. The fetuses were studied weekly until delivery. Real-time ultrasound examination of the fetus used a 3.5 or 5 mHz transducer. This took place in the afternoon 2 h after the woman had consumed a meal of 350 kcal and had not smoked for 4 h. FB activity was recorded on videotape during 1 h of observation. The total amount of time spent in FB activity was recorded using a stopwatch. Presence of FB was defined as breathing movements that lasted for >6 s with a breath-to-breath interval ≤ 6 s. In addition, episodes of sustained FB lasting >30 s were recorded. For the analysis of FB in relation to lethal lung hypoplasia, the last recording before birth was used. However, for the analysis of FB in relation to infection, only recordings obtained within 2 days of birth were used. The clinicians and the pathologist were unaware of the ultrasound findings. The diagnosis of lethal pulmonary hypoplasia at autopsy ($n = 2$) was based on a lung weight/birthweight ratio of ≤ 0.012 (Askenazi & Perlman 1979) or a radial alveolar count more than 1 SD below the mean for gestational age (Emery & Mithal 1960). Two pathologists examined at least two slides from uninflated lung specimens from each case. At least ten radial alveolar counts were done for each case. The pathologists' counts did not differ by more than 10% in each case. If autopsy was not performed ($n = 1$) the diagnosis of lethal pulmonary hypoplasia was based on the following clinical findings, small and bell shaped chest on x-ray, absence of infection, and no response to intratracheal instillation of surfactant. A four-quadrant assessment of amniotic fluid volume was made using a modification of the method by Phelan *et al.* (1987) and described by Rutherford *et al.* (1987). Since the gestational ages of our patients were less than those to which the technique was originally applied, the uterine cavity instead of the maternal abdomen was divided into four quadrants. The maximum vertical diameter of the largest fluid pocket was then measured in centimetres in each of the four

quadrants. Normal values for the gestational ages of our patients have not been established and for the purpose of this study we arbitrarily used the value of ≤ 5.0 cm as an abnormally low value. This value had been found to correlate significantly with fetal compromise at ≥ 36 weeks gestation (Rutherford *et al.* 1987). Surface and central bacterial cultures were obtained from all babies associated with PROM. Definite neonatal infections included sepsis, meningitis and bronchopneumonia as defined previously (Ohlsson *et al.* 1987). Bronchopulmonary dysplasia was defined as requiring additional oxygen at a corrected postnatal gestational age of 36 weeks (Shennan *et al.* 1988). Chorioamnionitis was defined, using a membrane roll, as infiltration with polymorphonuclear white blood cells in the chorioamnion. Funisitis was defined as infiltrations with polymorphonuclear cells into Wharton's jelly as seen on histological examination of a cross section of the umbilical cord. Sensitivity, specificity, positive and negative predictive values, and accuracy were calculated for the absence of FB in predicting chorioamnionitis/funisitis. Accuracy was defined as the sum of the true positives and true negatives divided by the total population (Sackett *et al.* 1985). Statistical analysis used the SystatTM software for Mac-Intosh IICxTM computer.

Results

The 23 fetuses were studied for a total of 46 h on 1–6 occasions. The mean gestational age at PROM was 25.7 weeks (range 18–30 weeks), the mean interval between PROM and delivery was 25 days (range 2–84 days), the mean gestational age at last examination was 28.5 weeks (range 23–33 weeks) and the mean gestational age at birth was 28.9 weeks (range 23–34 weeks). The median values for these variables are shown in Table 1 together with the clinical characteristics. Eight of the fetuses did not breathe at the last ultrasound examination, all other fetuses showed sustained fetal breathing for >6 s and of these all but one showed breathing for >30 s. One fetus, who previously had been breathing, did not breathe at the last examination and one fetus showed no fetal breathing movements on the first examination but was breathing at the next two examinations (Figure 1). Of the four perinatal deaths in the study, one was a stillbirth at 23 weeks and was not associated with pulmonary hypoplasia, the other three were due to pul-

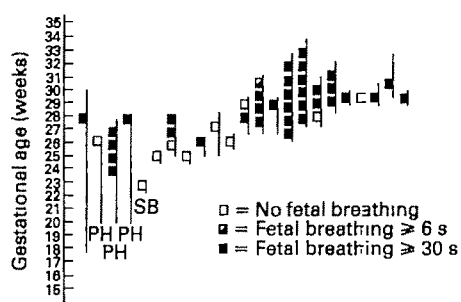


Fig. 1. Fetal breathing in relation to gestational age at rupture of membranes, latency period and outcome in 23 pregnancies. Each square represents 1 h of ultrasound observation for fetal breathing. The extremes of the vertical bars indicate gestational age at rupture of membranes and gestational age at delivery. PH = pulmonary hypoplasia. SB = stillbirth.

monary hypoplasia. One infant developed bronchopulmonary dysplasia. Seven infants received surfactant as part of a randomized controlled trial in the unit at the time of this study. Nine infants had limb contracture secondary to oligohydramnios. The amniotic fluid index was <5 cm in 16 pregnancies. Chorioamnionitis/funisitis was noted in 13 of 22 placentas examined (one placenta was not examined). Eight fetuses had a FB assessment within 2 days of delivery and all had their placentas examined. The sensitivity, specificity, positive and negative predictive values and the accuracy were all 75% for chorioamnionitis/funisitis in the absence of fetal breathing. The only baby with proven infection (bronchopneumonia and associated chorioamnionitis and funisitis) did not show FB activity when assessed 1 day before birth.

Discussion

In this pilot study in a population with a low prevalence of pulmonary hypoplasia, the absence of FB did not correlate with presence of this condition (Table 1, Figure 1). Therefore the assessment of FB, using our methods, was of no value in the prediction of lethal pulmonary hypoplasia.

It has been postulated that pulmonary hypoplasia could be due to inhibition of breathing movements (Gruenwald 1957; Wigglesworth *et al.* 1981). Two groups, one in New York, USA (Moessinger *et al.* 1984; Fox & Moessinger 1985; Moessinger *et al.* 1987) and one in London, England (Blott *et al.* 1987; Greenough *et al.*

1988, Blott & Greenough 1988) have studied FB in relation to lung hypoplasia. Moessinger *et al.* (1984) found that the frequency of FB movements was unchanged by amniotic fluid drainage at 117 days gestation in the sheep. Furthermore in two fetal preparations subjected to long term amniotic fluid drainage the frequency of FB activity was not affected. Fox & Moessinger (1985) reported FB activity in all seven human fetuses with prolonged oligohydramnios, but compared to matched control fetuses with normal amniotic fluid volume, they tended to spend less time breathing and did so at lower rates. The authors subsequently studied 14 pregnancies with oligohydramnios (4 with fetal anuria and 10 with PROM) and compared their FB activity with that in 45 matched controls with normal amniotic fluid volume (Moessinger *et al.* 1987). They defined an epoch of FB as beginning with a breath followed by two or more within a 6 s window. They found that FB activity had been present in all eight infants that died from pulmonary hypoplasia (diagnosed at post-mortem). Fetuses associated with PROM irrespective of outcome, spent the same or less time breathing compared with controls, whereas fetuses with renal anomalies associated with oligohydramnios and lung hypoplasia spent more time breathing than controls. The authors concluded that the observation of FB activity was not helpful in identifying pregnancies with oligohydramnios at risk of lung hypoplasia (Moessinger *et al.* 1987). Our findings are consistent with those of the New York group.

The London group has reported a series of 11 (Blott *et al.* 1987), 30 (Greenough *et al.* 1988) and 35 (Blott & Greenough 1988) pregnancies with PROM occurring at 15 to 26 (Blott *et al.* 1987), 15 to 28 (Blott & Greenough 1988) and 15 to 32 (Greenough *et al.* 1988) weeks gestation and where the duration of PROM was either >48 h (Blott *et al.* 1987), >1 week (Greenough *et al.* 1988) or >2 weeks (Blott & Greenough 1988). The authors did not give the dates for enrolment, nor did they state if these studies overlap, and why the inclusion criteria changed. They considered fetuses to be breathing only if an episode of FB movements was continuous for at least 60 s during a 30 min observation period (Greenough *et al.* 1988). In nine pregnancies there was an absence of FB movements and autopsy in eight of the nine infants revealed pulmonary hypoplasia. They concluded that the absence of FB movements was a reliable indi-

Table 1. Maternal, fetal and neonatal characteristics in 23 pregnancies

	Gestational age (weeks)			Duration of PROM (days)	FB activity (min/sec)	AFI (cm)	Contr-actures	Air-leaks	Outcome	Surfactant use	Chorio- amnionitis /funisitis
	At PROM	At delivery	At last FB study								
1.	18	30	29	84	13/0	4.5	+	-	Alive	+	-
2.	20	26	26	44	0/0	3.2	+	+	PH	-	+
3.	20	28	27	54	6/35	1.1	+	+	PH	+	-
4.	20	28	27	56	3/37	3.2	+	+	PH	-	-
5.	23	23	23	2	0/0	2.1	-	-	SB	-	+
6.	25	25	25	2	0/0	0.9	-	-	Alive	+	+
7.	25	29	29	30	15/20	0.6	+	+	BPD	-	+
8.	25	25	25	2	0/0	5.9	-	+	Alive	-	+
9.	25	26	26	5	2/06	1.9	-	-	Alive	-	n.a.
10.	25	28	27	22	0/0	1.9	-	-	Alive	-	+
11.	26	26	26	4	0/0	3.7	-	-	Alive	+	+
12.	27	29	29	16	0/0	3.5	-	-	Alive	-	+
13.	27	31	31	31	1/17	7.6	+	-	Alive	-	+
14.	27	29	28	14	2/53	4.5	+	-	Alive	-	-
15.	27	33	32	45	30/09	9.1	+	-	Alive	-	+
16.	28	34	33	48	28/34	11.4	-	-	Alive	-	-
17.	28	31	31	22	15/37	0.5	+	-	Alive	-	-
18.	28	32	32	30	20/47	7.3	-	-	Alive	+	-
19.	29	29	29	5	3/16	3.1	-	-	Alive	+	+
20.	29	29	29	3	0/0	3.2	-	-	Alive	+	-
21.	29	31	30	22	26/0	6.1	-	-	Alive	-	+
22.	30	33	31	26	7/46	7.4	-	-	Alive	-	+
23.	30	30	30	4	21/16	2.5	-	-	Alive	-	-
Median	27	29	29	22		3.2					

Abbreviations: PROM = prelabour rupture of the membranes. FB activity = total time spent in breathing activity; AFI = amniotic fluid index; PH = pulmonary hypoplasia, SB = stillbirth; BPD = bronchopulmonary dysplasia (alive), + present, - absent.

cator of lung hypoplasia (Greenough *et al.* 1988).

A possible explanation for these conflicting results may be the different definitions used for FB and pulmonary hypoplasia. Moessinger *et al.* (1987) used lung DNA content or lung/body weight ratio or both at autopsy, whereas Blott *et al.* (1988) used a lung/body weight ratio of ≤ 0.012 and a radial alveolar count (performed on inflated lungs) of ≤ 4.1 (Askenazi & Perlman 1979). We used a lung/birthweight ratio of ≤ 0.012 (Askenazi & Perlman 1979) or a radial alveolar count more than 1 SD below the normal value (for un-inflated lungs) for the corresponding gestational age according to Emery & Mithal (1960). According to Askenazi & Perlman (1979), the range for radial alveolar count using a modification of the method by Emery & Mithal (1960) is 4.1-6.3 at term (38 weeks) for un-inflated lungs. Blott & Greenough (1988) used the value of 4.1 on inflated lungs, even though all

the infants in their series were born at ≤ 35 weeks gestation. At this gestation 75% of the predicted value for the radial alveolar count for inflated lungs would be ≤ 3.0 (Cooney & Thurlbeck 1982). The higher cut-off point used by the London group could therefore have increased the prevalence of lung hypoplasia in their study thereby increasing the positive and negative predictive values of a FB activity test. The mean gestational age at PROM in the study reported by Blott & Greenough (1988) was also less (21.3 weeks, range 15-28 weeks) than in our series (25.7 weeks, range 18-30 weeks). In a separate study (Ohlsson *et al.* 1991) to assess the value of ultrasound measurements of fetal chest growth in the prediction of lethal pulmonary hypoplasia, we encountered no deaths from pulmonary hypoplasia in a series of 35 fetuses associated with PROM at >23 weeks gestation. Moessinger *et al.* (1987) studied fewer than four pregnancies with PROM at <24 weeks, whereas Blott &

Greenough (1988) followed 20 such pregnancies and we studied five. It is therefore possible that some of the differences in our results can be explained by different definitions of FB and different criteria for the diagnosis of pulmonary hypoplasia as well as differences in the true prevalence of pulmonary hypoplasia in the different study populations. Concomitant infection could also confound the results.

Our findings of a significant decrease in FB movements in fetuses associated with chorioamnionitis/funisitis support the findings by Goldstein *et al.* (1988) and Kivikoski *et al.* (1988). Goldstein *et al.* (1988) found that the absence of FB movements and gross body movements of <50 s duration was always associated with positive amniotic fluid cultures. Kivikoski *et al.* (1988) found that the frequency of FB movements, at between 28 and 41 weeks, was decreased in pregnancies associated with PROM (65%) compared with controls (90%). In a group with later evidence of amnionitis/neonatal infection, the frequency of FB movements was even lower than in the group with PROM only. The retrospective study by Vintzileos *et al.* (1986), which has been criticized elsewhere (Keirse *et al.* 1989; Ohlsson & Wang 1990), also suggested that the presence of FB activity is a good predictor of a noninfectious outcome (negative predictive value 95.3%), whereas its absence does not necessarily indicate impending infection (positive predictive value 50%).

We conclude that the absence of FB, as defined and measured in our pilot study in a population with a low prevalence of lethal pulmonary hypoplasia, is not of value in predicting the condition. Infants that die from pulmonary hypoplasia have early PROM, long standing oligohydramnios and show limb contracture at birth, but there are survivors associated with PROM of long duration. If further studies are planned, these should concentrate on a population with prolonged PROM at ≤ 24 weeks gestation. The lack of FB appears to be a better predictor of chorioamnionitis/funisitis, which is a complication often associated with prolonged PROM, and probably precedes fetal/neonatal infection. Goldstein *et al.* (1988) have suggested that interleukin-1 is secreted by the fetus in response to infection and results in decreased fetal activity. Based on the present pilot study, we recommend further studies of FB in relation to fetal/neonatal infections. However, there is a need for consensus among investigators regard-

ing the definitions of fetal breathing and diagnostic criteria for pulmonary hypoplasia.

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Maternal angiotensin sensitivity and fetal Doppler umbilical artery flow waveforms

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Summary. The angiotensin pressor response was investigated in normotensive pregnancies which had umbilical Doppler flow velocity waveforms suggestive of placental vascular disease. Of the 36 pregnancies studied at between 24 and 38 weeks gestation, 18 had a positive response to the angiotensin pressor test, these women were delivered earlier (35.3 vs 38.5 weeks, $P = 0.015$), had a lower mean birthweight centile (14 vs 36, $P < 0.001$) and higher frequency of fetal distress in labour (40% vs 7%, $P = 0.06$) when compared with the 18 women who had a negative response. The Doppler umbilical systolic-diastolic (S-D) ratio decreased with gestation in the negative group, suggesting continuing placental growth and vascular expansion, whereas the S-D ratio increased in the positive group ($P < 0.001$), indicative of vascular obliteration. We suggest that the positive angiotensin pressor response is primarily associated with the placental vascular pathology. Angiotensin infusion had no acute effect on maternal uteroplacental or fetal umbilical artery flow velocity waveforms.

During pregnancy, an abnormal pattern in the flow velocity waveform (FVW) of the umbilical artery identifies vascular pathology in the fetal placental circulation (Giles *et al.* 1985). The outstanding feature of this is a decrease in the small muscular arteries of the tertiary villi of the placenta but thickening and sclerosis are also noted in the remaining arterial vessels. It is suggested that this vascular lesion produces the increase in umbilical placental flow resistance. Since this placental lesion precedes evidence of fetal compromise, it is believed to cause the fetal effect with which it has been associated. Amongst

fetuses subsequently born small for gestational age (SGA), abnormal umbilical FVWs are present in two-thirds to three quarters (Trudinger *et al.* 1985a) and appear to identify those at greatest risk of antepartum hypoxaemia (Nicolaidis *et al.* 1988), perinatal asphyxia (Trudinger *et al.* 1987a), and neonatal complications (Hackett *et al.* 1987; Trudinger *et al.* 1990). An abnormal umbilical FVW is also a feature of severe pregnancy-induced hypertension (Trudinger *et al.* 1985b; Ducey *et al.* 1987). It is widely believed that in hypertensive disease of pregnancy a reduction in uteroplacental perfusion causes the frequently associated fetal deprivation (Gruenewald 1974). We have questioned this sequence because abnormal umbilical FVWs often precede overt disease and do not correlate with severity or duration (Trudinger & Cook 1990). We have suggested that the placental vascular lesion identified by abnormal umbilical FVWs might precede the clinical features of pre-eclampsia.

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Enhanced sensitivity to angiotensin infusion in contrast to the normal pregnancy refractoriness is one feature of pre-eclampsia known to precede the maternal disease and is believed to contribute to it (Gant *et al.* 1973). In this study we sought to clarify the relations between angiotensin sensitivity and the abnormal umbilical FVWs in a group of normotensive pregnancies identified by an abnormal umbilical FVW.

Subjects and methods

The study group comprised 36 women with a singleton pregnancy who had a Doppler umbilical FVW systolic diastolic ratio >95th centile, according to Thompson *et al.* (1988), on at least two occasions. This was a consecutive series of pregnant women referred to our laboratory for study, 14 of them were identified initially at their antenatal clinic visit by a programme that involved screening all pregnancies with Doppler at 28 weeks. The other 22 were referred to our laboratory by their obstetrician because of concern about fetal welfare. The gestational age ranged from 24 to 38 weeks. Women with hypertension at the time of Doppler study (sitting blood pressure >130/85 mmHg) were excluded from this study, as were those taking aspirin. Following the study, the women continued under the management of their obstetrician who had access to the results of the Doppler umbilical study, but not the angiotensin sensitivity test.

The angiotensin infusion sensitivity test (AIST) was based on the method described by Gant *et al.* (1973). The women lay in the right lateral position. An intravenous line was placed in a dorsal vein on the right hand. Blood pressure was recorded using an automated system (Dinamap) with the cuff applied around the left arm. Blood pressure readings were made at 2-min intervals and the study did not begin until the woman had relaxed and a constant basal pressure (three readings) was observed. Angiotensin (Hypertensin Ciba) was infused at an initial rate of 4 ng/kg/min and increased at 5-min intervals to a maximum rate of 20 ng/kg/min. A positive response was defined by an increase in diastolic blood pressure of >20 mmHg above the basal level at an infusion rate of <20 ng/kg/min. The positive result was confirmed by a second blood pressure reading before the infusion was ceased. Recordings of maternal blood pressure were continued after the infusion was ceased to reconfirm the basal reading. Our defi-

nition of a positive response was determined after studies of 25 normal pregnancies at 23–31 weeks gestation. Only five of these showed a pressor response at an infusion rate of <20 ng/kg/min but >12 ng/kg/min (none at <12 ng/kg/min).

Doppler FVWs were recorded as described by Trudinger *et al.* (1985a) from the umbilical artery and uteroplacental bed arteries before angiotensin infusion then during the infusion at 4, 12 and maximum ng/kg/min and again after the blood pressure had returned to basal level.

The women were followed until delivery and had FVWs recorded at least every 2 weeks. Pregnancy outcome was recorded on standard result sheets.

Statistical analysis

The angiotensin infusion sensitivity test was used to divide the women into a positive and negative group. These two groups were compared using the Mann Whitney *U* test for data not normally distributed relating to gestational age and Fisher's exact probability test for categorical data. Birthweight and placental weight were compared using an analysis of covariance in which the influence of gestational age was removed.

These studies were conducted with the approval of our institution's Research and Ethics Committees and informed consent was obtained from all the women.

Results

A total of 36 pregnant women were studied, 18 of them had a positive angiotensin pressor response (positive group), the other 18 formed the negative group. There were seven primigravida in each of the two groups. Table 1 details the pregnancy outcomes. Compared with the negative group, the women in the positive group were delivered earlier ($P = 0.015$) and their infants were smaller (corrected for gestation) ($P < 0.02$). The onset of labour was spontaneous in seven women in the negative group, but in only one in the positive group. Amongst women allowed to labour, fetal distress (repetitive late decelerations and/or scalp blood sample pH ≤ 7.20) was more frequent in the positive group ($P = 0.06$).

Doppler umbilical and uterine artery FVWs during angiotensin infusion are shown in Table 2. There were no effects of angiotensin on FVWs in any of the studies.

Table 1. Pregnancy outcome by angiotensin pressor response in 36 pregnancies with an abnormal umbilical artery Doppler flow velocity waveform

	Angiotensin pressor response		Significance
	Negative	Positive	
No. of women	18	18	
No. of primigravida	7	7	
Gestation (weeks)			
At AIST	30.1 (1.9)	31.3 (3.7)	ns*
At delivery	38.5 (2.3)	35.3 (4.0)	0.015*
AIST study—delivery interval (weeks)	8.5 (3.6)	4.0 (4.5)	<0.002*
Planned vaginal delivery	15	10	
Elective caesarean section	3	8	
Fetal distress in labour	1/15	4/10	0.06
Birthweight (g)	3048 (538)	2010 (966)	<0.02 †
Mean birthweight centile	36	14	<0.001*
No. SGA infants (<10th centile)	3	13	<0.001
Placental weight (g)	572 (168)	374 (162)	<0.05 †
Perinatal deaths			
Stillbirths	0	1	
Neonatal deaths	1	0	

Results are mean (SD) values where appropriate.

*Mann Whitney *U* test for non-normal data.

†*P* value from analysis of covariance after removing gestational age effect.

AIST = angiotensin infusion sensitivity test.

Subsequent Doppler umbilical artery FVWs in the pregnancies that continued for at least one week after the angiotensin pressor test were compared in the two groups. In the positive group, only 6 of the 16 pregnancies showed a

decrease in the FVW systolic diastolic ratio whereas in the negative group 15 of the 16 pregnancies showed the normal decrease ($P = 0.001$).

There were two perinatal losses. One stillbirth

Table 2. The effect of angiotensin infusion on fetal umbilical and maternal uteroplacental artery flow velocity waveforms systolic diastolic ratios

Artery	Time of study	Systolic diastolic ratio		
		Whole group	Positive AIST	Negative AIST
Umbilical		(<i>n</i> = 36)	(<i>n</i> = 18)	(<i>n</i> = 18)
	Before infusion	5.63 (1.75)	6.40 (2.13)	4.86 (0.69)
	During infusion of			
	4 ng/kg/min	5.36 (1.90)	6.20 (2.30)	4.52 (0.80)
	12 ng/kg/min*	5.26 (1.95)	6.09 (2.36)	4.43 (0.86)
Uteroplacental†	After infusion	5.20 (1.74)	6.00 (2.07)	4.40 (0.78)
		(<i>n</i> = 20)	(<i>n</i> = 9)	(<i>n</i> = 11)
	Before infusion	1.69 (0.56)	1.88 (0.81)	1.54 (0.12)
	During infusion of			
	4 ng/kg/min	1.68 (0.56)	1.84 (0.82)	1.54 (0.11)
	12 ng/kg/min*	1.67 (0.56)	1.83 (0.82)	1.53 (0.12)
	After infusion	1.67 (0.56)	1.86 (0.81)	1.52 (0.11)

Results are mean (SD) values.

*In those patients who were positive at an infusion rate of less than 12 ng/kg/min, this study was done at the maximum infusion rate.

†As the women lay on their right side the uteroplacental circulation was accessible in only 20.

AIST = angiotensin infusion sensitivity test.

occurred at 26.4 weeks in the positive group; the fetus weighed 345 g and delivery had not been effected because of the small fetal size. The other was a neonatal death in the negative group and was associated with a truncus arteriosus anomaly.

Discussion

Our study demonstrates that amongst normotensive pregnant women with a high umbilical artery systolic diastolic ratio, a positive angiotensin infusion sensitivity test (pressor response) predicts those at risk of the fetal morbidity traditionally associated with 'placental insufficiency'. In contrast, the negative angiotensin response indicating normal pregnancy refractoriness was associated with good fetal outcome in terms of fetal growth, size at birth, and freedom from fetal distress in labour. Subsequent umbilical Doppler studies in the negative group showed the normal trend of a decreasing systolic diastolic ratio even if above the 95th centile value. We suggest this indicates normal growth and expansion of the umbilical placental vascular bed in the negative group. In this study, we simplified classification of angiotensin responsiveness by dividing the study population into two groups, based on their pressor response. Significant correlations existed between the actual pressor dosage of angiotensin and the outcome indices.

This study provides important information about the interpretation of a high umbilical artery systolic diastolic ratio. We have suggested this is due to a reduced number of small arteries in the umbilical placental vascular bed. Using a mathematical model of the placenta in which detailed attention was paid to the vascular branching of the umbilical placental villous tree, we have recreated the flow velocity waveforms seen in both normal and complicated pregnancy (Thompson & Trudinger 1990). The waveform pattern associated with a high systolic diastolic ratio was reproduced by reducing the number of small arterial branches in the villus tree. This theoretical demonstration matches the observation of a reduced tertiary villus arterial count in the placentas of pregnancies in which the abnormal waveform is present (Giles *et al.* 1985). Experimentally, vascular embolization has been used to reduce the vascular branching of the umbilical placental circulation and produced the same alteration in the waveform pat-

tern (Trudinger *et al.* 1987b). A reduced vascular umbilical placental bed could result from either acquired disease or a 'small' normal placenta. We suggest that the 'small' placenta is present in those pregnancies in which a high systolic diastolic ratio waveform pattern is found, but subsequent fetal outcome is normal with no suggestion of fetal compromise. With advancing gestation, serial Doppler studies in these pregnancies would be expected to show the normal decrease in systolic diastolic ratio as the placenta grows normally. In the present study a negative angiotensin pressor response was associated with good fetal outcome. These pregnancies would represent as false positives in a population study using umbilical Doppler. The positive angiotensin pressor response group are the true positives. They exhibited the fetal morbidity associated with placental insufficiency and the increasing systolic diastolic ratio suggesting progressive vascular pathology in the placenta. To confirm this speculation it will be necessary for us to now examine placental histology in such pregnancies. It is not possible from our study to ascertain whether the positive AIST precedes or follows the vascular pathology in the placenta.

Although we excluded women with hypertension from our study, the findings are relevant when considering the origins of pre-eclampsia and placental insufficiency. In high risk pregnancy abnormal umbilical Doppler flow velocity waveforms have been associated with fetal compromise and hypertensive disease of pregnancy. Pre-eclampsia is known to be preceded by a positive AIST. Angiotensin sensitivity has been implicated in the origin of the maternal hypertension. It has also been suggested that hypertension contributes to the vascular pathology in the placental bed (Robertson *et al.* 1975). In the present study only one of the positive AIST group later developed hypertension. This indicates that the positive angiotensin infusion sensitivity test is primarily associated with the umbilical placental pathology that leads to fetal compromise. Pre-eclampsia would seem to be secondary to these two phenomena. We hypothesize that it is the placental lesion detected by umbilical Doppler studies that is the primary event and pre-eclampsia occurs only in a subgroup of these pregnancies in which the woman is predisposed in some way. A possible criticism of this hypothesis is the occurrence of pre-eclampsia in some pregnancies with normal Doppler studies. Using the mathematical model

of the placenta described above we have shown that 60–80% of small arterial channels need to be occluded before the umbilical velocity waveform becomes abnormal (Thompson & Trudinger 1990). In these anomalous cases with a normal Doppler, we suggest that the extent of the pathology does not reach this degree before the woman develops the pre-eclamptic response to the presence of the placental pathology.

There has been much recent interest in the use of low dose aspirin therapy in pregnancy. Studies have shown this treatment prevents pregnancy hypertension (Beaufils *et al.* 1985; Wallenburg *et al.* 1986) and improves fetal outcome in women with a poor past obstetric history (Wallenburg & Rotmans 1987). We have demonstrated that aspirin given to women with a high umbilical systolic diastolic ratio results in improved fetal and placental growth (Trudinger *et al.* 1988). We suggest that aspirin arrests progression of the placental vascular lesion. If the fetal placental lesion precedes the maternal hypertension, then the beneficial effects of aspirin in preventing hypertension (pre-eclampsia) can be explained by the effect of aspirin on the fetal placental lesion.

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Vulvar vestibulitis syndrome: a clinico-pathological study

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Summary. Twenty four patients with the vulvar vestibulitis syndrome formed the basis of this clinicopathological study. Entry dyspareunia was the constant presenting complaint and vestibular erythema with acute superficial tenderness the invariable clinical finding. In our series there was a marked predominance of Caucasians, patients were most often of social classes I and II and most frequently in the third decade. The results of laboratory investigation revealed that this syndrome has a diverse range of potential aetiologies including vulval infections, dysplasia and in one instance acute vasculitis.

Although vulval discomfort with dyspareunia has been recognized as a distinct clinical entity for over a century (Skene 1889) it has received scant attention in the literature until this last decade. The renewed interest has coincided with an apparent rising prevalence, noted especially in North America (Reid *et al.* 1988).

The terminology for chronic vulval pain is still a source of controversy. Thus McKay (1988) suggested the term vulvodynia to be applied to all cases of vulval pain, regardless of aetiology, but Lynch (1986) considered that this term should be applied only to those cases which lacked a demonstrable aetiology. Friedrich (1987) described a triad of presenting features which he named the vulvar vestibulitis syndrome. These included (i) severe pain on attempted vaginal entry (ii) tenderness to pressure localized within the vulval vestibule and (iii) physical findings

confined to vestibular erythema of variable degree.

The aetiology of this clinical syndrome remains unknown. Its association with a preceding candidal infection has suggested a hypersensitivity reaction, or an irritant or allergic reaction to topical therapy. This has been refuted by other authors although they have not provided a satisfactory alternative hypothesis (Marinoff & Turner 1986). The demonstration of human papilloma virus by DNA hybridization techniques (Turner & Marinoff 1988) has implicated a sub-clinical wart virus infection as another potential cause of this syndrome. Histopathological investigations have been of little help in elucidating the pathogenesis. A non-specific chronic inflammatory cell infiltrate within the lamina propria and squamous metaplasia of the vestibular glands have been the most frequent reported findings. Pyka *et al.* (1988).

The incidence and prevalence is not known but it is certainly not an uncommon disorder.

Clinical features

We have assessed 24 consecutive patients fulfilling Friedrich's criteria for vulvar vestibulitis syndrome.

In addition to a full clinical and in particular

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dermatological examination, patients had a detailed vulvo-vaginal assessment. Routine microbiological investigations were performed. Samples were taken from the vaginal wall for yeast and clue cells and cultured for *Candida* species. Secretion from the posterior fornix was examined by microscopy and cultured for *Trichomonas vaginalis*. A cervical smear was taken from each patient for cytological examination. Samples were taken from the urethra and endocervix for *Neisseria gonorrhoea* and secretion from the cervical os for *Chlamydia trachomatis*. Each patient had a superficial excisional biopsy of an area of maximum tenderness within the vulval vestibule. Follow-up care was provided by the gynaecologists or by ourselves, depending on the histopathological findings.

Most of the patients were ≤ 30 years of age, 19 (79%) were aged between 21 and 30 years, four between 30 and 40 years and only one was in the sixth decade. Most of the patients (92%) were Caucasian. One was Afro-Caribbean and one was of Mediterranean origin. All except three belonged to social classes I and II. All but one claimed to have had one regular sexual partner of at least 6 months' duration. One patient was virgo-intacta.

All patients had had multiple out-patient appointments and visits to their general practitioners. One patient was thought to have recur-

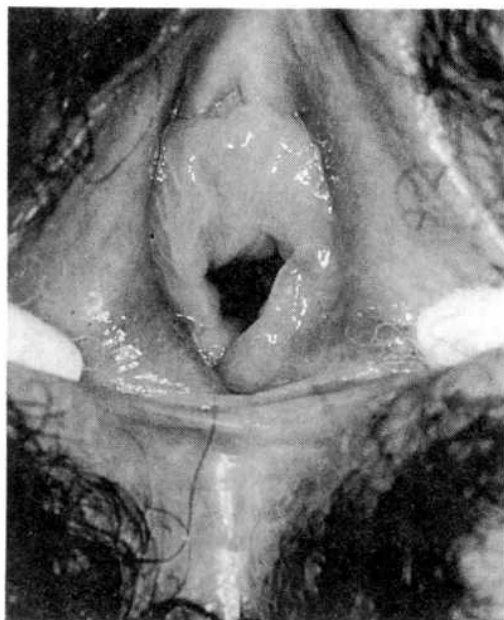


Fig. 1. Vulvar vestibulitis: vulva showing swelling and erythema.

rent herpes simplex infection but this was never confirmed virologically. Candidiasis was the most frequent clinical diagnosis but this was confirmed by culture in only six patients. Anaerobic vaginosis, pelvic inflammatory disease and psychosexual problems were occasional diagnoses.

Entry dyspareunia and painful coitus was invariably a presenting complaint. It was described as severe and burning. Often it was associated with diminished frequency of coitus. Post-coital burning persisted for 1–24 h. Pain also occurred on insertion of tampons, during washing, micturition, on wearing tight clothing and frequently spontaneously. Symptoms had persisted for >6 months in 92% of patients. In 25% of patients it had been present in excess of 2 years.

Clinical examination revealed local vestibular erythema and oedema characteristically in the region of the minor vestibular gland ostia (Fig. 1). Acute superficial tenderness on palpation was invariably present. One patient had a clinical wart and another a superficial abscess.

Candida was cultured in 6 (25%) patients. Clue cells were found in four. *C. trachomatis* was isolated in one patient. Cervical cytology were normal in all smears.

Pathological findings

The histopathological features were variable (Table 1). Most commonly seen was the non-specific finding of epithelial hyperplasia accompanied by an acute or chronic inflammatory cell infiltrate in the lamina propria (Fig. 2). This is probably of doubtful significance. Six patients had dysplasia (Fig. 3) of the surface epithelium. In three there was an associated koilocytosis (Fig. 4) and two patients had koilocytosis without dysplasia. In two patients there was acute inflammation involving the sebaceous glands. In one patient an inflamed condyloma acuminatum was seen and in another the features of a neutrophilic vasculitis was present. In one patient no significant pathology was found.

Table 1. Histopathological findings in 24 women with vulvar vestibulitis syndrome

Non-specific chronic inflammation	11
Epithelial dysplasia	6
Inflammation of sebaceous glands	2
Koilocytosis without dysplasia	2
Inflamed viral wart	1
Neutrophilic vasculitis	1
No significant pathology	1

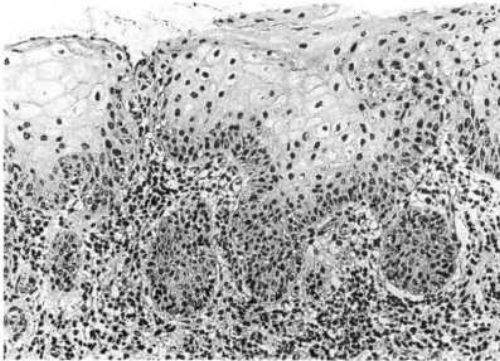


Fig. 2. Hyperplastic vulval surface epithelium. A dense chronic inflammatory cell infiltrate is present in the lamina propria.

Special stains for micro-organisms were negative.

Discussion

The vulvar vestibulitis syndrome characteristically develops in sexually active young white women. It frequently affects professionals typically in whom relationships are apparently stable and monogamous.

There is a marked preponderance of Caucasian patients in our series compared to the general clinic at St. Thomas' Hospital where 40% of patients are Afro-Caribbean and 60% Caucasians. A similar unexpected absence of black patients from a mixed population in Florida was noted by Friedrich (1987). This disparity in the prevalence of vulvar vestibulitis syndrome in white compared to black patients suggests that there might be a genetic predisposition, or alternatively marked socio-cultural differences in responses to the disease manifestations.

When findings are negative, presumptive

diagnoses are often made. All too frequently a diagnosis of 'recurrent candidiasis' is made, often in spite of repeated negative cultures. Other presumptive diagnoses are anaerobic vaginosis and pelvic inflammatory disease, with the result that the patient receives unsuccessful treatment with various anti-candidal regimens and antibiotics. The vulvar vestibulitis syndrome has well defined clinical characteristics. All patients with persistent vulvar pain need thorough examination, including biopsy even if they have had proven candidal infection.

We were particularly interested in the variable pathological features of the mucosa and lamina propria in this syndrome. The consistent clinical features of the vulvar vestibulitis syndrome in association with the diverse histopathological findings suggest that the vulvar vestibulitis syndrome may well be the end point of a number of pathological processes. The initiating event may be an infection or trauma such as parturition, but the cause of the perpetuation of the inflammatory response remains undetermined. Further investigation is indicated to unravel this aspect of the disease process.

Epithelial dysplasia, accompanied by koilocytosis, was the second commonest histological finding in our series. Although this may be a reflection of the high prevalence of human papilloma virus and its sequelae within the general population, it is nevertheless an important observation and, whatever its importance in the pathogenesis of the vulvar vestibulitis syndrome, it is obviously an indicator for long term gynaecological monitoring.

The presence of clue cells, suggestive of *Gardnerella vaginalis*, and chlamydial infection, imply that other infections may have aetiological importance. It is noteworthy that no patient in

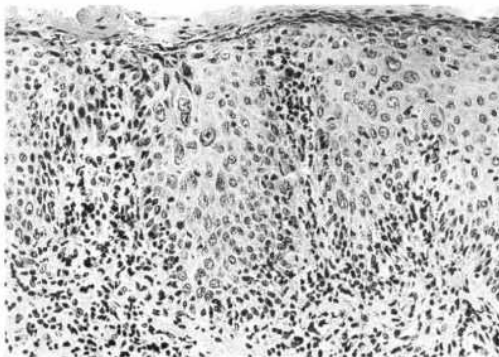


Fig. 3. Vulvar vestibulitis syndrome showing parakeratosis. The epithelium is disorganized and shows lack of maturation and nuclear pleomorphism.

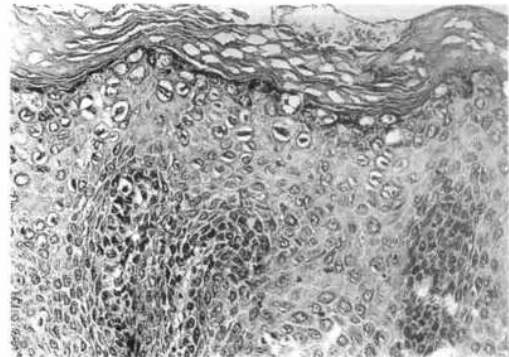


Fig. 4. Abundant keratohyalin granules and vacuolation of the superficial keratinocytes indicate of human papillomavirus infection.

our series was found to be suffering from the other commonly occurring sexually transmitted diseases such as *T. vaginalis* or *N. gonorrhoea*.

Two of our patients have been reviewed by the gynaecologists. Colposcopic biopsy revealed mild dysplasia (CIN I).

The natural history of this disease is unknown. Long term follow-up of these patients is commonly necessary. Repeat biopsy may on occasion provide a rational basis for therapy.

The prognosis for these patients has always been poor. Thorough examination, accurate diagnosis and counselling will often alleviate a great deal of suffering. It is important that these patients are not labelled neurotic and just dumped into the nearest available clinical 'garbage can' in an effort to shed the responsibility of dealing with a chronic and as yet potentially insoluble problem.

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A comparative study of ethamsylate and mefenamic acid in dysfunctional uterine bleeding

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Summary. The effects of ethamsylate and mefenamic acid on menstrual blood loss were compared in a double-blind trial in 34 women with menorrhagia. Both drugs produced statistically significant reductions in blood loss during the 3 months of treatment; the overall reduction was 20% in the ethamsylate group and 24% in the mefenamic acid group. Compared with pretreatment values, blood loss was significantly less in each of the 3 treatment months in the mefenamic acid group, but only in the second and third months of treatment in the ethamsylate group. However, more women had a clinically useful reduction in blood loss (>40%) in the ethamsylate group. The onset of effect of mefenamic acid was rapid but ethamsylate showed a comparatively greater effect as the trial progressed. Cessation of treatment was followed by an increase in blood loss, more pronounced in mefenamic acid group who reverted to pre-treatment levels. A greater number of side-effects were reported with mefenamic acid.

Menorrhagia is a common clinical problem. Normal monthly menstrual blood loss is about 35 ml with a 90th centile value of 80 ml. Menstrual loss in excess of 80 ml is widely accepted as an objective definition of menorrhagia (Hallberg *et al.* 1966). Both ethamsylate (Harrison & Campbell 1976; Jaffé & Wickham 1973; Kovacs & Annus 1978) and mefenamic acid (Anderson *et al.* 1976, 1979; Haynes *et al.* 1980; Fraser *et al.* 1981) are used as non-hormonal treatments

especially for ovulatory dysfunctional uterine haemorrhage.

As there had been no direct comparison between ethamsylate and mefenamic acid, the aim of this study was to compare the effects of these treatments.

Subjects and methods

Women aged 18-55, with menorrhagia and regular menstrual cycles, were admitted to the study after receiving a full explanation and giving informed consent. Their measured blood loss had to exceed 80 ml during at least one of two pre-treatment cycles to qualify for admission.

Malignant disease had been excluded previously by dilatation and curettage or Vabra curettage and a minimum of 3 months had elapsed between the curettage and entry in to the trial.

Women were excluded from the study if they:

(i) were taking oral contraceptives, silicone-

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based antacids, coumarin anticoagulants or protein bound drugs, (ii) had known hepatic impairment, inflammatory bowel disease or endocrine disorders, (iii) might wish to become pregnant during the trial, (iv) had known allergies to inhibitors of prostaglandin synthesis; (v) were anaemic (haemoglobin <9 g/dl); (vi) were fitted with an intrauterine contraceptive device; (vii) had notable uterine enlargement due to fibroids.

The women were allocated to treatment groups by minimization (Taves 1974) with the objective of matching for age and the severity and duration of menorrhagia. The women received either ethamsylate (500 mg four times daily) or mefenamic acid (500 mg three times daily) administered orally as tablets and capsules, respectively, on a double-blind double-dummy basis since the appearance of the two products could not be matched. All the women received both 'treatments' (i.e., tablets and capsules) but one of these was a placebo. Therefore both the subjects and staff were unaware which was the active drug.

Treatment was started on the first day of bleeding and continued until the end of bleeding.

Throughout the study, all women used sanitary towels and tampons which were collected regularly from their homes by our research sisters. Blood loss was assessed by an aqueous extraction procedure from the sanitary material followed by colorimetric measurement of alkaline haematin at 550 nm, as described by Newton *et al.* (1977).

Blood loss was measured during each of three consecutive treatment cycles. Treatment was then withdrawn and blood loss was measured during the following menstrual cycle to determine the effect of treatment withdrawal.

Side effects possibly attributable to treatment were assessed at each visit and their severity was recorded on a four-point scale: 1 = mild, not

reported spontaneously but only after questioning, 2 = moderate, reported spontaneously; 3 = severe, requiring a reduction of dosage; 4 = very severe, requiring termination of treatment with the trial drug.

For statistical calculations, the data were computerized. Paired *t*-tests were used for differences within treatment groups and Student's *t*-tests for differences between treatment groups.

Results

In total, 44 women entered the study. Results are reported for the 34 women who actually completed the trial, 16 of them received ethamsylate and the other 18 mefenamic acid. Ten women did not complete the trial and were excluded from the analysis; six (three from each group) withdrew without starting treatment and a further three (one given mefenamic acid and two given ethamsylate) withdrew after only one month for reasons apparently unrelated to treatment. One woman was given ethamsylate withdrew after she started treatment because she developed hot flushes and diarrhoea. These withdrawals had the effect of unbalancing the previously minimized groups where mean pretreatment blood losses had been 150 ml (± 64 ml) and 134 ml (± 50 ml) in the ethamsylate and mefenamic acid groups respectively. As shown in Table 1, after drop-outs the pretreatment blood loss was 33% higher in patients allocated to receive ethamsylate. The difference, compared with the mefenamic acid group, was not statistically significant ($P = 0.108$). As the amount of blood loss in the two pretreatment months did not differ significantly the two values were combined. Blood losses during the treatment period have been compared with the respective mean pretreatment values and have been expressed in percentage terms to facilitate comparison between the groups.

Table 1. Mean pretreatment blood loss in women with menorrhagia allocated to receive either ethamsylate or mefenamic acid

Treatment group	Blood loss (ml) (mean $\pm$ 95% confidence limit)		
	Pretreatment month 1	Pretreatment month 2	Mean of two pretreatment periods
Ethamsylate ($n = 16$)	188 $\pm$ 54	212 $\pm$ 72	200 $\pm$ 56
Mefenamic acid ($n = 18$)	141 $\pm$ 50	145 $\pm$ 53	143 $\pm$ 50

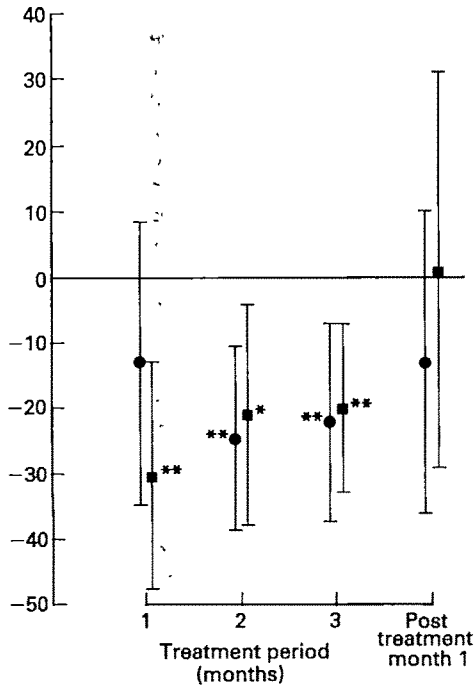


Fig. 1. Reduction in blood loss, as a percentage of mean treatment values attributable to ethamsylate (●) or mefenamic acid (■) during 3 months of treatment and 1 month after treatment. The vertical bars represent the mean $\pm$ 95% confidence intervals. Compared with pretreatment values. * $P < 0.05$, ** $P < 0.01$.

Over the total 3-month treatment period, both drugs produced a statistically significant reduction in monthly blood loss ($P < 0.02$) followed by a return towards pretreatment values when drug administration was discontinued (Fig. 1).

On a month-by-month basis, the reduction in blood loss was statistically significant in the ethamsylate-group during treatment months 2 and 3 ($P < 0.01$) and in the mefenamic acid group in each of the 3 treatment months ($P < 0.01$, $P < 0.05$ and $P < 0.01$, respectively). There were,

however, no significant differences between the two treatment groups in any month.

The results in Fig. 1 are expressed as mean $\pm$ 95% confidence intervals and indicate where the upper limits of probability relate to reductions in blood loss by potentially clinically useful values of 10–40%. Indeed, the longer-term usefulness of ethamsylate is indicated by the larger numbers of women showing clinically significant reductions in blood loss of $\geq 40\%$ compared with mefenamic acid, in month 3 (Table 2).

In the month immediately after the treatment ended, blood losses increased in both groups and were similar to pre-treatment values. The mean post-treatment blood loss in the mefenamic acid group was within 1% of the pretreatment value, but in the ethamsylate group the loss was equivalent to that after the first month's treatment (Fig. 1).

To assess the performance of each of the drugs, the regressions of mean blood loss in the total treatment period over those of the pre-treatment period were calculated and in both treatment groups there was a significant correlation between these two measures (ethamsylate: during vs pre-treatment, $r^2 = 0.771$, $P < 0.001$; mefenamic acid during vs pre-treatment, $r^2 = 0.765$, $P < 0.01$), indicating that both drugs are similarly effective in treating a range of blood loss.

Side effects

Of the 34 patients, 15 reported side effects. Of the 18 women in the mefenamic acid group 10 (56%) had side effects of which 6 (60%) were scored ≥ 2 . In the ethamsylate group, 5 of 16 (31%) reported side effects, of which 3 (60%) were scored ≥ 2 . The difference in the occurrence of side effects was not statistically significant ($\chi^2 = 2.03$, $P = 0.16$). No side effects in either treatment group led to cessation of treat-

Table 2. Number of women showing specified percentage of blood loss in second and third months of treatment

Reduction in blood loss (%)	Second month		Third month	
	Ethamsylate (n = 16)	Mefenamic acid (n = 18)	Ethamsylate (n = 16)	Mefenamic acid (n = 18)
10–30	5 (31)	6 (33)	3 (19)	8 (44)
30–40	0 (0)	4 (22)	2 (13)	3 (17)
>40	6 (38)	4 (22)	6 (38)*	2 (11)*

* $P = 0.08$

Results are numbers of women with % in parenthesis

ment. The commonest side effects in both groups were nausea, backache and a bloated abdomen. In the ethamsylate group the reported side effects were abdominal discomfort in two, headache in two and backache in one. In the mefenamic acid group the side effects were abdominal discomfort in four, headache in four, tiredness in one and swollen ankles in one.

Discussion

In this study clinically useful reductions in blood loss were noted with both mefenamic acid and ethamsylate. The results compare favourably with the results reported by others (Fraser *et al.* 1981; Harrison & Campbell 1976).

Month-by-month results (Fig. 1) indicate that compared with pretreatment values, mefenamic acid produced its maximum effect in the first month of treatment whereas ethamsylate seemed to produce its maximum effect in the second and third months. Both drugs were well tolerated and no patient withdrew because of side effects.

Previous studies with mefenamic acid have shown reduced blood loss in women with menorrhagia, but the extent of the reduction appears to be variable. Average reductions of 37% (Anderson *et al.* 1976) and 44.5% (Haynes *et al.* 1980) have been reported but the range of individual response is large (Anderson *et al.* 1979). In a series of 69 women with a mean menstrual blood loss of 67 ml, an overall reduction of 28% was seen after treatment with mefenamic acid and in a sub-group of 30 women with pre-treatment losses of 110 ml, there was a 30% reduction (Fraser *et al.* 1981).

Ethamsylate also shows an inhibition of the prostaglandin pathway (Kovacs & Falkay 1981) but appears to act at a different enzymatic point from other non-steroidal anti-inflammatory drugs (Rennie & Lam 1989). In contrast to aspirin, ethamsylate does not increase bleeding time (Hutton *et al.* 1986).

In a double-blind placebo-controlled trial of ethamsylate, Jaffé & Wickham (1973) reported a significant reduction (20%) in the number of tampons used and also in the duration of bleeding. Harrison & Campbell (1976) reported significant reductions in blood loss of 50% and 19% in women with primary menorrhagia and intrauterine contraceptive device-induced menorrhagia, respectively. In each subgroup, the authors reported a linear relation between menstrual

loss with placebo and the reduction in blood loss on ethamsylate treatment, indicating that ethamsylate may be used to treat patients with small or large blood losses with equivalent effectiveness. In the present study, ethamsylate appeared to confirm this as patients in the ethamsylate group have larger pre-treatment blood loss (Table I).

Mefenamic acid significantly reduced the blood loss (compared with pre-treatment) in all 3 months, the maximum effect being in the first month while ethamsylate appeared to produce more clinically useful reductions in blood loss of >40% as the trial progressed.

Although this study was carried out over a limited time, these results suggest that treatment with both preparations might possibly be more effective than using one treatment alone: for example, using mefenamic acid to cover first month followed by the effect of ethamsylate in the second and third months. However, a further trial over a longer time would be required to test this hypothesis.

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Quantitative production of prostaglandin E₂ and its metabolites by human fetal membranes

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Summary. Cultured amnion, choriodecidua and intact fetal membrane produced similar quantities of prostaglandin E₂ (PGE₂) (1-5 ng/ml). Choriodecidua and intact fetal membrane also produced very high levels of PGE₂ metabolites (100-1000 ng/ml). The total production of PGE (PGE₂+PGE₂ metabolites) was similar in intact fetal membrane and in choriodecidua, suggesting that the amnion, although a source of PGE₂, contributes little to the overall PGE production by fetal membranes.

The prostaglandins PGE₂ and PGF_{2α} have been implicated in the process of human labour (MacDonald *et al.* 1978), and it is accepted that the fetal membranes are a major source of these compounds (Keirse & Turnbull 1976). The production of primary prostaglandins (PGE₂ and PGF_{2α}) as well as their inactive metabolites by separated amnion, chorion and decidua has shown that these tissues produce different prostaglandins and have different metabolic capacities. The amnion produces mainly PGE₂ and only low levels of PGF_{2α} and the inactive metabolites (Okazaki *et al.* 1981; Skinner & Challis, 1985; Warrick *et al.* 1985; Cheung & Challis, 1989). The chorion contains enzymes that rapidly metabolise prostaglandins (Keirse

& Turnbull 1976) and produces low levels of PGE₂ and PGF_{2α}, together with high levels of their metabolites (Okazaki *et al.* 1981; Skinner & Challis, 1985; Warrick *et al.* 1985; Lopez Bernal *et al.* 1987). These results may be contrasted with those obtained with the decidua, which produces higher levels of primary prostaglandins than the chorion (Okazaki *et al.* 1981; Skinner & Challis, 1985; Warrick *et al.* 1985; Lopez Bernal *et al.* 1987) as well as the inactive metabolites (Casey *et al.* 1989a). No quantitative data seem to be available on the production of PGE₂ and its metabolites by intact fetal membrane and the individual components of the fetal membrane, so it is difficult to assess which of the tissues in the fetal membrane produces most PGE₂. Also, the tissues in the fetal membrane may interact with each other and the overall production of PGE₂ and its metabolites may not be the sum of the production from each component of the membrane. The objective of this study was to assess the quantitative production of PGE₂ and its metabolites by different fetal membrane components, to gain further insights into which parts of the fetal membrane release the largest quantities of PGE₂. Separated chorion and decidua could not be obtained without causing major changes in tissue structure, so intact fetal membrane, amnion and choriodecidua were investigated.

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Methods

Fetal membranes were obtained from normal pregnancies after delivery by elective caesarean section before the onset of labour. Intact fetal membrane, amnion or choriondecidua were cultured as described previously (Roseblade *et al.* 1990). Briefly, intact fetal membranes, amnion or choriondecidua were placed over the ends of glass cylinders (diameter 1.4 cm) and held in place with a rubber ring. Excess tissue was removed with a scalpel blade and the membranes were cultured in 12-well tissue culture plates at 37°C in 95% air; 5% CO₂. Medium 199, containing 10% horse serum and 1% glutamine (all from GIBCO), was used for all tissue culture. The medium on the fetal side of the membrane was separated from that on the maternal side, and could be analysed separately for eicosanoid production. The membranes were incubated for 24 h to decrease spontaneous prostaglandin production in response to the stresses of delivery and the setting up of tissue culture. Fresh medium was then added and the incubations continued for various times up to 24 h. The medium was frozen at -20°C until analysis for PGE₂ and its metabolites by radioimmunoassay. PGE₂ was measured with an in-house assay (PGE₂ antibody from ICN Biomedical, 3H-PGE₂ from Amersham International and standard PGE₂ from Sigma) and a commercial kit (Amersham International) was used to measure enzymic metabolites of PGE₂, namely 13,14-dihydro-15-keto-PGE₂ (PGE₂m) and 13,14-dihydro-15-keto-PGA₂ (PGA₂m). The antibody to PGE₂ had a cross-reactivity of <0.01% with the PGE₂ metabolites mentioned above, and the antibody to PGE₂ metabolites had a cross-reactivity of <0.001% with PGE₂. Student's *t*-test was used to investigate differences in prostaglandin production.

Results

The production of PGE₂ by intact fetal membranes, by amnion and by choriondecidua is shown in Table 1. The levels are similar to those reported previously, and there was a gradual time-dependent increase in PGE₂ production by the intact fetal membrane and by the chorion. PGE₂ production was similar in the different tissues and there were no statistically significant differences in PGE₂ production between the fetal and maternal sides of the membrane.

Very high levels of PGE₂ metabolites were

produced by intact fetal membrane and by choriondecidua (Table 2), and PGE₂ metabolite levels were undetectable when amnion alone was cultured (results not shown). Similar levels of PGE₂ metabolites were produced by choriondecidua and by intact fetal membrane at all time points except after 24 h incubation (Table 2). The total production of PGE (PGE₂+PGE₂ metabolites) was essentially that of PGE₂ metabolites since this was 100-fold higher than PGE₂ levels. It was apparent that total PGE production by amnion was far less than that of choriondecidua or intact fetal membrane. Lower levels of PGE₂ metabolites were found on the decidual side of the membranes at all incubation times except after 24 h of culture (Table 2), suggesting that equilibration of the PGE₂ metabolites may have occurred by this time.

Discussion

The production of PGE₂ by fetal membranes and the cells thereof has been extensively investigated and found to be of the order of 1–5 ng/10⁶ cells or per ml culture medium (Skinner & Challis 1985; Warrick *et al.* 1985; Lopez Bernal *et al.* 1987; McCoshen *et al.* 1987), but there seem to be no data on the production of PGE₂ metabolites under similar conditions. This is surprising since it is well known that the chorion can readily metabolise PGE₂ (Keirse & Turnbull 1976), and will thus affect the levels of PGE₂ found. The data reported here show that large quantities of PGE₂ are produced in a time-dependent way by intact fetal membrane and by choriondecidua, and that the majority of this PGE₂ is metabolized enzymically by the 15-keto-dehydrogenase and 13,14-reductase enzymes. The amnion produces relatively small quantities of PGE₂; overall total choriondecidual PGE₂ production outweighs that of the amnion by >100-fold.

It has been demonstrated that the chorion produces little PGE₂ (Warrick *et al.* 1985), but our results indicate that levels of PGE₂ were similar on both sides of the choriondecidua (Table 1). We suggest that this PGE₂ may originate in the decidua, but further experiments are needed to investigate this possibility. If so, this would imply that the decidua is a major intrauterine source of PGE₂. In our fetal membrane culture system the chorion metabolizes >98% of this production, so damage to the chorion could affect intrauterine PGE₂ levels by decreasing the metabolism of PGE₂. The importance of the

Table 1. Production of prostaglandin E₂ (PGE₂) by fetal membrane components (fetal and maternal sides) after different incubation times

Incubation time (h)	Side	PGE ₂ production (ng/ml)		
		Intact (n=6)	Choriodecidua (n=6)	Amnion (n=4)
2	Fetal	1.1 (0.7)	1.2 (0.4)	2.3 (0.5)
	Maternal	1.3 (0.7)	2.5 (0.7)	0.8 (0.2)
5	Fetal	1.8 (0.7)	n.d.	2.6 (0.3)
	Maternal	1.4 (0.6)	n.d.	1.7 (0.4)
10	Fetal	1.5 (0.4)	n.d.	1.6 (0.2)
	Maternal	1.9 (0.5)	n.d.	0.9 (0.2)
16	Fetal	2.4 (0.5)	2.5 (0.4)	3.1 (0.3)
	Maternal	2.6 (1.0)	1.4 (0.5)	3.2 (1.3)
24	Fetal	6.3 (1.2)*	0.9 (0.4)	2.2 (0.3)
	Maternal	3.9 (1.4)	2.1 (1.2)	4.8 (1.4)

Results are means (SEM) values, not all time points were examined within each experiment

Significance of difference. * = $P < 0.05$ compared with other tissues after the same length of incubation. n.d. = not done.

chorion in modulating PGE₂ output by the fetal membrane may be assessed by considering the effect of changing the metabolic capacity of the chorion. A 1% decrease in metabolism would increase PGE₂ levels 2–3 fold, and a 5% decrease would elevate PGE₂ levels to 10–50 ng/ml (depending on incubation time). These levels are similar to those detected in amniotic fluid during labour, so it remains a possibility that changes in the metabolic capacity of the chorion may be as important as any stimulation of PGE₂ production in the initiation of labour.

The size of the change (only 5%) suggested by these figures is such that detection would be difficult, but consideration should be given to this problem. The effect of the metabolic capacity of the chorion on labour will also be uncertain since any decidual prostaglandin production has immediate access to the myometrium. It is therefore conceivable that decidual prostaglandin production is of importance during labour. A recent report on the association between pre-term labour and intrauterine infection also implicates the decidua in labour (Casey *et al.*

Table 2. Production of prostaglandin E₂ (PGE₂) metabolites by fetal membrane components (fetal and maternal sides) after different incubation times

Incubation time (h)	Side	PGE ₂ metabolite production (ng/ml)	
		Intact	Choriodecidua
2	Fetal	209 (58)*	234 (62)*
	Maternal	92 (31)	157 (24)
4	Fetal	237 (37)*	n.d.
	Maternal	135 (41)	n.d.
16	Fetal	n.d.	776 (116)*
	Maternal	n.d.	484 (79)
21	Fetal	954 (115)*	n.d.
	Maternal	580 (76)	n.d.
24	Fetal	1041 (216)	323 (77)**
	Maternal	829 (237)	229 (62)**

Results are means (SEM) values. Not all time points were examined within each experiment (16–24 h points, $n=3$; 2–4 h points, $n=7$)

Significance of difference: * = $P < 0.05$ compared with the decidual side of the fetal membrane. ** = $P < 0.05$ compared with intact fetal membranes incubated for the same period of time. n.d. = not done.

1989b), so further studies on the role of the decidua are required.

The only clear-cut difference between intact fetal membrane and choriodecidua was that much lower levels of PGE₂ metabolites were produced by choriodecidua after 24 h of incubation. The significance of this is unclear, but in the absence of any dramatic changes in PGE₂ levels it would suggest a general decrease in PGE₂ production rather than a change in the metabolic capacity of the chorion. This may be related to the absence of amnion and indicate some form of interaction between the different components of the fetal membrane, but this needs to be investigated more fully.

In conclusion, the decidua seems to be the quantitatively major source of PGE₂ from the intrauterine tissues. The control of PGE₂ production from this tissue therefore requires investigation.

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The role of postnatal x-ray pelvimetry after caesarean section in the management of subsequent delivery

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Summary. The purpose of this study was to investigate the influence of postnatal x-ray pelvimetry after caesarean section on the management of the subsequent pregnancy. The case records of 331 women delivered by caesarean section in their first pregnancy were reviewed. By standard radiological criteria, the pelvis was considered to be inadequate in 248 (75%) of them and adequate in 83 (25%). Of the women with a radiologically inadequate pelvis, 172 underwent an elective caesarean section. Seventy-six were allowed vaginal delivery: 51 of these women delivered vaginally and 25 required an emergency caesarean section. Of the women with a radiologically adequate pelvis, 61 achieved a vaginal delivery and 22 were delivered by caesarean section. All of the three cases of uterine rupture occurred in women with a radiologically adequate pelvis. This study suggests that x-ray pelvimetry is not a good predictor of the outcome of a trial of vaginal delivery. We conclude that the practice of routine postnatal pelvimetry should be abandoned.

For women delivered by caesarean section, postnatal x-ray pelvimetry is performed routinely in many obstetric units in the United Kingdom. This investigation plays a major role in deciding the mode of delivery in subsequent pregnancies. Many obstetricians believe that radiological inadequacy of the pelvis contraindicates vaginal delivery because of an increased risk of uterine rupture. As a result, an elective caesarean section is often considered the safest method of delivery despite evidence suggesting that in over 75% vaginal birth can be expected after cae-

sarean section (Paul *et al.* 1985; Meier & Porreco 1982; Lavin *et al.* 1982). The inaccuracies of postnatal pelvimetry have been described (Varner *et al.* 1980; Fine *et al.* 1980; Barton *et al.* 1982), the investigation suffers from technical and physiological pitfalls. Among radiologists there is little consensus of opinion about which method of obtaining pelvic measurements is most appropriate and clinically useful (Nielsen *et al.* 1985). The technique provides static information and misses the physiological changes in fetal and pelvic shape which normally occur in labour.

The aim of this study was to investigate the role of postnatal x-ray pelvimetry following caesarean section. Our objective was to assess the influence of this technique on the obstetric management of the subsequent pregnancy.

Subjects and methods

Between 1977 and 1982, 1620 postnatal pelvi-

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Table 1. Recommended minimum pelvic measurements for vaginal delivery according to Russell & Richards*

	Normal population value (cm) Mean (SD)	Minimum advised (cm)
Sagittal inlet	11.8 (1.1)	11 or BPD +0.5
Maximum transverse of inlet	12.8 (0.76)	11.5
Outlet		
Bispinous	10.4 (0.86)	9.0
Sagittal outlet	11.6 (1.1)	10.0

*Reproduced with permission from Russell (1973) *Radiology in Obstetrics and Antenatal Paediatrics*, Butterworth & Co.

BPD = biparietal diameter.

metries were performed at Glasgow Royal Maternity Hospital. The case records of primigravida patients who had a caesarean section and postnatal x-ray pelvimetry during this period were examined and from these, 331 women were selected because their second pregnancy was managed in the same obstetric unit.

Pelvimetry measurements were obtained from two pelvic x-rays: coronal diameters were measured from an antero-posterior view of the pelvis using the orthodiagraphic shift method (Milne 1966) and sagittal measurements were taken from an erect lateral view with a notched ruler in the natal cleft. The radiologists' interpretation of the adequacy of the pelvis according to the recommended minimum value for vaginal delivery by Russell & Richards (1971), shown in Table 1, was recorded.

From the obstetric records we noted the birthweight in both pregnancies, the obstetrician's decision concerning management of the patient's second delivery and actual mode of delivery. We examined the influence of the x-ray results on the obstetrician's management of the second pregnancy and the relation between the radiological findings and outcome.

Results

Of the 331 case records studied, 248 (75%) were found to have had a radiologically inadequate pelvis. Vaginal delivery was planned for 68 of the

248 women considered to have an inadequate pelvis and elective caesarean section was planned for the remaining 180 women; in 139 of them the decision was based on pelvimetry alone; in 40 women there were additional contributing factors and one woman requested an elective caesarean section. Vaginal delivery was planned for 79 of the 83 women with a radiologically adequate pelvis, the other four requested a caesarean section.

Table 2 shows the actual mode of delivery in relation to pelvimetry results. Seventy-six women with a radiologically inadequate pelvis (including eight for whom an elective caesarean section was originally planned) were allowed a trial of labour because the obstetrician responsible for their care questioned the value of postnatal pelvimetry. There was no significant difference in the pelvic dimensions between these women and the other 172 who were delivered by elective section. Considering the women who were allowed a trial labour, the proportion of those who achieved a vaginal delivery was not significantly different whether the pelvis had been considered radiologically adequate or inadequate (Fisher's exact test $P = 0.11$). Birthweight in the first and second pregnancies was compared in relation to the mode of delivery in the second pregnancy. The mean birthweight in the women who had a failed trial of vaginal delivery was greater than in those delivered vaginally and also greater than in their first preg-

Table 2. Actual mode of delivery in relation to pelvimetry results

Mode of delivery	Inadequate pelvis ($n = 248$)	Adequate pelvis ($n = 83$)	Total
Elective section	172	4	176
Trial of vaginal delivery			
Emergency section	25	18	43
Vaginal delivery	51	61	112

nancy but neither difference was statistically significant.

Discussion

Radiological measurement of pelvic diameters has been widely used to decide the appropriate method of delivery when the capacity of the pelvis is in doubt. Most studies assessing this technique relate to the role of antepartum pelvimetry (Varner *et al.* 1980; Fine *et al.* 1980; Barton *et al.* 1982). Our study considers specifically the role of postnatal pelvimetry after caesarean section. Pelvimetry had a significant influence on the planned mode of delivery in the subsequent pregnancy and 73% of the women with a radiologically inadequate pelvis were managed by elective caesarean section on the basis of pelvimetry alone. Obstetric management should only be based on the results of an x-ray examination if that investigation is reliable. The fallibility of pelvimetry is demonstrated by our study in that 51 of the 76 women who had a radiologically inadequate pelvis and were allowed a trial labour achieved a vaginal delivery. Conversely 18 of the 79 women with an adequate pelvis required an emergency caesarean section.

It has been suggested that one of the major benefits of pelvimetry is the identification of women at particular risk of scar rupture in a subsequent labour (Thoms 1941). Our experience does not support this suggestion. Three women in our study had scar dehiscence. All three were allowed a trial of vaginal delivery after being assessed as having a radiologically adequate pelvis.

Pelvimetry is maternally focused and does not assess fetal size and presentation. Furthermore, it is a static examination which does not take account of changes in pelvic and fetal dimensions during labour and delivery.

Our data also show that 72% of women who were allowed a trial labour were delivered vaginally, regardless of whether the pelvis was thought to be radiologically adequate or not. This figure is in keeping with recent reports on the success rate of a trial of vaginal delivery after primary caesarean section (Paul *et al.* 1985; Meier & Porreco 1982; Lavin *et al.* 1982). We speculate that of the 132 women in whom the decision to deliver by caesarean section was made on the basis of pelvimetry alone, 88 would

have achieved a vaginal delivery if they had been given the opportunity.

Postnatal pelvimetry after caesarean section would not appear to be useful in the management of the subsequent delivery. Vaginal delivery can be achieved in the majority regardless of the pelvimetry results. An adequate result does not eliminate the risk of uterine rupture. We suggest that postnatal pelvimetry should be abandoned. In the absence of other obstetric indications for caesarean section, all patients should be allowed a trial of labour in a subsequent pregnancy.

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Pregnancy after orthotopic liver transplantation. Case report

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Case report

The patient, born in 1959, initially presented aged 9 years with an acute hepatitis-like illness, originally attributed to hepatitis A. She then developed ascites and a diagnosis of lupoid chronic active hepatitis with cirrhosis was made. Her smooth muscle and anti-nuclear antibodies were subsequently positive. Menarche occurred age 15 and after a short period of oligomenorrhoea, she developed amenorrhoea. Throughout this period her liver condition remained stable on low dose prednisolone. Aged 25 she attended the infertility clinic where ovulation was induced with clomiphene citrate 100 mg. All infertility investigations were normal, apart from a persistently elevated testosterone concentration of 10.9-21.0 nmol/l (normal range 0.5-2.5 nmol/l); the androstenedione concentrations were normal. Despite regular ovulatory cycles she failed to conceive and had unsuccessful attempts at both IVF and GIFT.

Aged 30, she became increasingly lethargic and later developed spontaneous bleeding from the urinary tract and gums. Her serum albumin fell to below 30 g/dl and an orthotopic liver transplant was performed on 24th May 1989. Her post-operative recovery was complicated by a biliary leak, after removal of the T-tube, and a laparotomy was performed on 12th August

1989, recovery was otherwise uneventful. Immunosuppression was maintained with reducing doses of prednisolone, azathioprine 100 mg daily, and cyclosporin A 150 mg twice daily. Subsequent to the transplant, her menstruation returned and she conceived spontaneously 4 months post-operatively. Throughout pregnancy she was maintained on azathioprine 100 mg, cyclosporin A 175 mg twice daily, and ranitidine 150 mg daily. She was admitted at 12 weeks gestation with vaginal bleeding, but this settled with rest in bed. When seen for booking, she was mildly hypertensive with a blood pressure of 140/95 mmHg, but the serum AFP and ultrasound scan were both normal. She continued to be hypertensive throughout pregnancy with diastolic blood pressures ranging from 85 to 105 mmHg. Regular liver function and haematological tests, and serial ultrasound scans for growth were all normal. She was admitted at 14 and 26 weeks gestation with tenderness in the right upper quadrant of the abdomen. On both occasions she had no nausea or vomiting, the liver function tests were normal and there was no evidence of rejection. She was later admitted at 36 weeks gestation because of increasing abdominal tenderness and suspected intrauterine fetal growth retardation. The fetal heart rate recordings were normal and an elective caesarean section was performed at 38 weeks gestation because of increasing abdominal tenderness and an unfavourable cervix.

The male fetus weighed 2560 g (10th centile) and had Apgar scores of 9 and 10 at 1 and 5 min, respectively. There was no evidence of any congenital abnormalities. The mother's post-operative recovery was uneventful and both mother and baby were discharged one week after operation. When seen 6 weeks later for postnatal examination, menstruation had already occurred spontaneously. A hormone profile was

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normal, and the testosterone concentration had returned to normal.

Discussion

Since the first human liver transplant in 1963, liver transplantation has become an established treatment for chronic liver disease, acute liver failure and certain metabolic defects (Burroughs & Rolles, 1990). With improving survival rates, the indications for liver transplantation have widened, and consequently an increased number of pregnancies in women after liver transplantation will occur. Clinical experience related to pregnancy after renal transplantation has demonstrated the possibility and safety of pregnancy following transplantation, but clinical experience after liver transplantation is much more limited. Walcott *et al.* (1978) described the first successful pregnancy after liver transplantation, but since then there have been only nine further publications. The present case is the 13th pregnancy associated with liver transplantation to be reported, but only the third in the United Kingdom. Amenorrhoea is a well recognized complication of all types of severe chronic liver disease. Cundy *et al.* (1990) reported a prevalence of amenorrhoea of 48% in women with chronic liver disease prior to transplantation,

but this was reversed within 10 months of surgery in 97%. The hormonal basis for this amenorrhoea is poorly understood and has been thought to be due to hypothalamic-pituitary dysfunction, but in none of the previously reported cases was the serum testosterone estimated. In women, the liver is responsible for metabolizing the testosterone produced (Kirschner & Bardin, 1972; Johnson, 1984), and in our case the serum testosterone was markedly elevated during the period of amenorrhoea. Although the testosterone concentration was not measured post-operatively, because the patient became pregnant so soon after transplantation, it had returned to normal postnatally when she once again started to menstruate. It is therefore possible that the amenorrhoea associated with chronic liver disease may in part be secondary to the failure of the diseased liver to metabolize testosterone.

With the introduction of cyclosporin in 1981, a marked improvement in survival rates after liver transplantation occurred (Iwatsuki *et al.* 1988) and the drug has been used in 9 of the 13 reported pregnancies (Table 1). However, cyclosporin is nephrotoxic and almost 40% of patients taking cyclosporin will develop hypertension in pregnancy (Winter *et al.* 1990). The drug has also been reported as a cause of intra-uterine growth retardation in 56% of preg-

Table 1. Reported pregnancies after liver transplantation

Pregnancy no.	Case report	Months after transplant	Con-ception	Mode of delivery	Gestation (weeks)	Birth-weight (kg)	Drugs	Aetiology
1	Walcott <i>et al.</i> (1978)	27	Assisted	Forceps	40	2.4	A/P	BC
2	Myers <i>et al.</i> (1980)	57	Assisted	SVD	40	2.5	A/P	BC
3	Newton <i>et al.</i> (1988)	120	Assisted	Abruption	28	1.1	A/P	CAH
4	Venkataramanan <i>et al.</i> (1988)	16	Spont	SVD	40	3.2	C/P	PBC
5	Venkataramanan <i>et al.</i> (1988)	12	Spont	SVD	36	1.7	C/P	CIRR
6	Haagsma <i>et al.</i> (1989)	4	Spont	LSCS	38	2.2	A/C/P	CIRR
7	Sims <i>et al.</i> (1989)	36	Spont	SVD	38	2.7	C	CAH
8	Alvin <i>et al.</i> (1989)	18	Spont	SVD	39	3.1	C	CAH
9	Cundy <i>et al.</i> (1990)	15	Spont	IUD	24	?	A/C/P	CIRR
10	Cundy <i>et al.</i> (1990)	5	Spont	SVD (twins)	34	?	C/P	CAH
11	Winter <i>et al.</i> (1990)	48	Spont	LSCS	33	1.9	C	CIRR
12	Hutton & Wyeth (1990)	23	Spont	LSCS	27	1.0	A/C/P	2°BC
13	Present report	4	Spont	LSCS	38	2.5	A/C/P	CAH

Abbreviations. A = azathioprine; C = cyclosporin; P = prednisolone, PBC = primary biliary cirrhosis; CAH = autoimmune (lupid) cirrhosis; CIRR = cryptogenic cirrhosis; BC = Budd Chiari, 2°BC = secondary biliary cirrhosis. SVD = spontaneous vaginal, IUD = intrauterine death; LSCS = lower segment caesarean section. Pregnancies 1 and 2 occurred in the same woman.

nancies after renal transplantation (Pickrell *et al.* 1988) and in 50% after liver transplantation (Table 1). There was one intrauterine fetal death associated with cyclosporin (Cundy *et al.* 1990). This is thought to be related to drug induced vasoconstriction. Because of the potential risks to the fetus, it is possible that maintenance immunosuppression during pregnancy should be with prednisolone and azathioprine only. Obviously one must balance the risks to the fetus of cyclosporin therapy against the risks to the mother of graft rejection, but it is clear that when cyclosporin is used in pregnancy, fetal growth must be closely monitored.

After liver transplantation, menstruation and subsequent fertility can return quite rapidly, indeed our patient conceived within 4 months of operation and five of the ten spontaneous conceptions after liver transplantation occurred within 12 months of operation (Table 1). This further emphasizes the need for contraception counselling for all patients, and contraception should be used from the time of resuming sexual intercourse, even if menstruation has not yet returned. Although the oral contraceptive pill can be considered for most patients after liver transplantation, it should not be advised in those with the Budd-Chiari syndrome. It is probably advisable for the recipient to wait a full year after liver transplantation before conceiving, as this is the period at highest risk of graft complications.

Our experience with this patient, and with reviewing the published literature, suggests that pregnancy is not contraindicated after liver transplantation.

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Congenital afibrinogenaemia and successful pregnancy outcome. Case report

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Case report

The successful outcome of pregnancy in a 25-year-old woman with congenital afibrinogenaemia is discussed. She had been found to have afibrinogenaemia soon after birth, following investigation for severe bleeding from her cord stump. She frequently suffered with severe bruising, heavy menstruation and excessive bleeding after dental treatment. She had had an average of two to three fibrinogen transfusions a year at the time of acute bleeding episodes such as following tooth extraction, appendicectomy or for a heavy period. Her first pregnancy in August 1988 miscarried at 7 weeks gestation with excessive bleeding. Her fibrinogen level was undetectable. She was transfused with fibrinogen prior to the evacuation of retained products of conception. Her second pregnancy followed soon after (March 1989), and was complicated with multiple episodes of bleeding from the 5th to 13th week, during which time she received intermittent fibrinogen transfusions.

Repeated weekly 5 gm fibrinogen transfusions from the 13th week served to halt the bleeding, but premature separation of the placenta at 27 weeks gestation resulted in preterm labour and the birth of a live 610 g baby, who died shortly afterwards. Her pre- and post-fibrinogen transfusion levels during this pregnancy varied between 1 and 100 mg/dl and the level was 0.9 mg/dl on the day of the placental abruption. After this tragic episode it was decided she should have prophylactic fibrinogen transfusions during the next pregnancy. To avoid the incon-

venience of repeated hospital admissions the patient was taught to give her own fibrinogen infusions at home. She infused 5 g fibrinogen every 8-10 days at home. She conceived after about 2 months of starting this treatment and, from 7 weeks of pregnancy, she was followed up by both obstetrician and haematologist every 2 weeks and 1 week, respectively. It was decided to maintain a fibrinogen level of at least 100 mg/dl during pregnancy and 150 mg/dl during labour. This was achieved by thrice weekly infusions of 7 g of fibrinogen, increasing to 10 g as gestation increased. An extra 10 g of fibrinogen was given at the time of induction of labour.

Assessment of fetal growth and wellbeing was undertaken by repeated ultrasound and Doppler studies. As fetal growth was normal and there was no bleeding, pregnancy was continued to the 39th week of gestation. Labour was induced on 20 August 1990 using prostaglandin E₂ vaginally, artificial rupture of the membranes and oxytocin. An epidural anaesthetic was given during labour. A low cavity forceps delivery was necessary because of delayed progress in the second stage and resulted in the birth of a healthy male baby of 3550 g. The patient returned home on the third postnatal day with advice to continue fibrinogen infusions at a reduced dose of 5 g thrice weekly for a further 4 weeks. She had a normal puerperium and was completely well at 6 weeks after delivery.

Discussion

Congenital afibrinogenaemia was first described by Rabe & Solomen (1920). Since then approximately 150 cases have been reported. It is an autosomal recessive disorder affecting males and females in equal proportions.

This is the second reported case of congenital afibrinogenaemia in the world literature with a successful pregnancy outcome; and it is the first

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to end with a vaginal delivery at term. The previous successful pregnancy was managed by Inamoto *et al.* (1985) and ended in caesarean section at 37 weeks gestation.

The successful management of these two pregnancies confirms that fibrinogen is important in the maintenance of normal pregnancy. Several cases have been reported previously by various authors in which failure to complete a normal pregnancy has been ascribed to a deficiency of fibrinogen, using terms such as afibrinogenaemia (Evron *et al.* 1985); hypofibrinogenaemia (Hahn *et al.* 1978; Aznar *et al.* 1970; Pritchard 1961); dysfibrinogenaemia, or deficiency of factor XIII (fibrin stabilizing factor) necessary for cross linking of fibrin (Egbring *et al.* 1970; Fisher *et al.* 1966).

The exact role played by fibrinogen in maintaining pregnancy is not well defined but the hypothesis developed by Pritchard (1961) is attractive. He suggested that minute placental separation and haemorrhages occur in a normal pregnancy and are controlled by prompt conversion of maternal fibrinogen to fibrin. The hyperfibrinogenaemia of normal pregnancy maintains the integrity of placental implantation and in women with fibrinogen deficiency, the protection may be lacking. Leidholm *et al.* (1975) suggested that normal fibrinogen seems to play a significant role in implantation. Penn *et al.* (1971) produced a high rate of fetal absorption in animal models with hypofibrinogenaemia.

As our patient conceived easily on two occasions without the administration of fibrinogen it may be that fibrinogen is not so important during implantation but is necessary for continuation of the pregnancy. There have been no reported cases of afibrinogenaemia where the pregnancy has advanced more than a few weeks without treatment. Recurrent miscarriage with afibrinogenaemia has been described by Evron *et al.* (1985). The minimum plasma level of fibrinogen required for a successful pregnancy is not yet known. A value of 60 mg/dl has been suggested by Inamoto *et al.* (1985). The levels resulting from therapy must be high enough to prevent recurrent miscarriage (Aznar *et al.* 1970; Hahn *et al.* 1978) and premature separation of the placenta (Ness *et al.* 1983; Pritchard *et al.* 1961).

Although repeated fibrinogen/cryoprecipitate transfusions carry the risk of infection with the hepatitis B and HIV viruses and the possibility of fibrinogen antibody production, alloimmunization, uncontrollable haemorrhage at a later date

and an exaggerated thrombotic response, it is the only hope of achieving a successful pregnancy. Our patient was given fibrinogen concentrate in preference to cryoprecipitate because it can be stored at room temperature and is therefore ideal for home treatment (cryoprecipitate must be stored at -20°C).

Because the half life of fibrinogen is only 48 h frequent infusion is needed. To overcome the inconvenience of frequent hospital visits our patient was trained before conception to inject her own fibrinogen at home. The fibrinogen level was maintained at ≥ 100 mg/dl by thrice weekly infusions. Increasing amounts of fibrinogen were needed as the pregnancy progressed to maintain this level. The amount used was increased gradually from 18 g weekly in early pregnancy to 30 g weekly at term. The fibrinogen requirement falls sharply after delivery. Our patient needed only 15 g weekly to maintain the same level during the puerperium.

We feel that in the absence of associated obstetric complications it is reasonable to allow pregnancy to continue to term. Induction of labour was preferred to spontaneous onset to ensure that delivery was effected in planned conditions with the full support of the haematological team. Post partum haemorrhage is a real danger (Ratten *et al.* 1969; Strickland *et al.* 1982). According to Gilabert *et al.* (1987) a minimum fibrinogen level of 120 mg/dl is required for haemostatic protection during delivery. We gave an extra 10 gm of fibrinogen during induction to maintain a fibrinogen level above 150 mg/dl.

Epidural analgesia is possible provided normal fibrinogen levels are maintained. As the condition is an autosomal recessive the fetus is very unlikely to have a similar disorder. Vaginal delivery should be the aim but, as there is no increased risk of intracranial haemorrhage due to a bleeding diathesis, instrumental delivery is acceptable. A high level of fibrinogen should be maintained during the puerperium as delayed post partum haemorrhage (Strickland *et al.* 1982) has been reported in a patient with hypofibrinogenaemia. Our patient continued fibrinogen therapy for 4 weeks post partum.

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A maternal death caused by AIDS. Case report

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Case report

A 26-year-old Ugandan woman presented at 10 weeks gestation in her second pregnancy to a district general hospital casualty department, complaining of shortness of breath on exertion, fevers and a productive cough for 1 week. Six years previously she had had an uneventful pregnancy and vaginal delivery. She had not booked for antenatal care in her present pregnancy as she had arrived in Britain as a political refugee only 2 weeks previously. Initial physical examination revealed tachypnoea (70/min) and pyrexia. Her chest X-ray was suggestive of an interstitial pneumonia. Arterial blood gases, on air, showed a P_{O_2} of 10.0 kPa. She was treated with intravenous ampicillin and erythromycin for 3 days but she continued to deteriorate. A blood sample was then taken to test for human immunodeficiency virus (HIV) antibody, after the patient was counselled, and the result was found to be positive. A presumptive diagnosis of *Pneumocystis carinii* pneumonia (pneumocystosis) was made, which was confirmed by monoclonal antibody staining of a sputum specimen. Treatment was started with intravenous Septrin (trimethoprim-sulphamethoxazole), 1.8 g every 6 h, and hydrocortisone, 100 mg every 12 h. However, the patient's condition deteriorated and after 10 days of this therapy her P_{O_2} on 60%

oxygen was 7.4 kPa and she was transferred to this unit.

On admission, the Septrin therapy was changed to intravenous pentamidine and oral rifampicin, 600 mg/day, and isoniazid, 100 mg three times daily were started to prevent possible reactivation of tuberculosis due to the concurrent corticosteroid therapy.

A blood sample was taken and the results showed a white cell count of $28.7 \times 10^9/l$ and a haemoglobin concentration of 8.2 g/dl. Serum biochemistry was within normal limits and blood cultures were negative, including culture for *Mycobacterium*. Although a termination of pregnancy was considered at the patient's request, she was considered unfit for general anaesthesia. The patient's condition continued to deteriorate, despite further therapy with Eflornithine (DFMO), 400 mg/kg/day as a continuous infusion, and she died on the 24th day after presentation.

Discussion

This case represents the first maternal death associated with HIV infection to be reported in Britain and raises two interesting questions

First, did the delay in the diagnosis of HIV seropositivity affect the outcome? The patient's HIV antibody status was unknown before admission and this led to a delay in the initiation of appropriate therapy. Furthermore she had not had the opportunity to receive any pre-pregnancy counselling regarding the interaction of HIV infection and pregnancy. As the largest American study of deaths in pregnant HIV seropositive women found that 80% were due to pneumocystosis (Koonin *et al.* 1989), the use of prophylaxis in this group of patients needs to be considered. Although several regimens have been shown to be effective in reducing the risk of pneumocystosis in immunocompromised patients with HIV infection, the Centres for

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Disease Control have advised against their use in pregnant women because of the potential adverse effects on the fetus (CDC 1989). The drug of choice for prophylaxis is oral Septrin. Although both components of this drug cross the placenta, neither drug appears to be teratogenic (Minkoff *et al.* 1989). Inhaled pentamidine isethionate is reserved, in our practice, for those patients who are intolerant of Septrin. It is a potential teratogen as it has been shown to inhibit protein and nucleic acid synthesis in vitro (Drake *et al.* 1985), although it has been shown not to increase chromosomal aberrations (McDiarmid *et al.* 1989). Furthermore, its delivery by nebulized administration produces low or undetectable plasma levels (Girard *et al.* 1989).

In non-pregnant patients the risk of developing pneumocystosis is related to CD4 lymphocyte counts. At a level of less than 200/mm³, 8.4% of the patients will develop pneumocystosis within 6 months, at 12 months 18.4% and at 36 months 33.3% (Polk *et al.* 1987). However, Biggar *et al.* (1989) have shown that HIV antibody positive women exhibit a greater and more sustained fall in CD4 lymphocyte cell counts during pregnancy compared with seronegative pregnant women. Thus it may be argued that prophylaxis should start earlier in pregnant women than in other immunocompromised patients. We feel that prophylaxis needs to be individualized to suit the best needs of the patient. Likewise, with regard to the treatment in this case by Eflornithine: this is a second line drug sometimes used as salvage therapy (Smith *et al.* 1990). As in the above argument, the potential advantages to the mother must be weighed against the potential disadvantages to the fetus, particularly as Eflornithine is a contragestational agent (Fozard *et al.* 1987). In spite of that we felt that the patient's deteriorating condition warranted its use.

Secondly, as this patient's illness was unusual both in its severity and in the lack of response to treatment, the question also arises as to whether this was related to her pregnancy. While some authors feel that pregnancy may accelerate the progress of HIV infection (Deschamps *et al.* 1989; Delfraissy *et al.* 1989), others do not (Bradbeer 1989). Studies of whether or not particular opportunistic infections may have a more protracted or severe course in pregnancy are awaited.

If pregnancy does confer an increased risk of

severe opportunistic infection, then the question of termination of pregnancy becomes more important. If the delayed recovery of post-partum CD4 cell counts in HIV infected women (Biggar *et al.* 1989) are comparable to the situation after abortion, then no immediate benefit may be seen on survival. As this patient was unfit for anaesthesia, termination by antiprogesterone agents, e.g., RU486, may have been advantageous.

This case report presents the first maternal death due to AIDS in an HIV seropositive woman in Britain. However, as the prevalence of HIV infection in women in the UK is increasing (Communicable Disease Report 1990) this association may be seen far more commonly in future maternal mortality reports. The management of HIV-associated opportunistic infections in pregnancy needs to be carefully assessed, but due to the current paucity of numbers this will require multi-centre collaboration. In the interim, obstetricians and gynaecologists will need to be aware of these potential problems which may befall their patients.

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Overlap syndrome and its implications in pregnancy. Case report

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Case report

A 29-year-old woman booked for her second pregnancy at 16 weeks gestation. At 2 years of age she had developed a seronegative juvenile chronic arthritis (Still's disease) requiring steroid therapy. Various corrective orthopaedic procedures had been performed in childhood, including staple insertions in both knees, correction of a valgus deformity and bilateral hip replacements. Steroids were stopped when she was 16 years of age, and her joint disease had been quiescent for over 10 years. However, a strongly positive anti-nuclear antibody titre had been noted with a raised IgG and a persistently raised ESR 7 years previously, although there was no evidence of active lupus.

There had been no problems in the first pregnancy: labour had started spontaneously at 36 weeks, and she was delivered by elective caesarean section because of her extensive joint deformity and a suspicion of cephalopelvic disproportion. Intubation was reported to be difficult, but the procedure was otherwise uneventful, with the birth of a healthy 2.5 kg girl.

In this pregnancy all appeared well at booking, and an ultrasound scan confirmed her dates. At 30 weeks she was admitted in labour. There was a persistent fetal bradycardia of 80 beats/min, the maternal pulse being 100/min. The cervix was tightly closed. An ultrasound scan demonstrated an active, normally grown baby

with heart block. The heart appeared normal in structure. On the basis of this assessment intravenous ritodrine was started and dexamethasone was given to promote fetal lung maturation; her labour did not progress. A subsequent ultrasound scan confirmed normal cardiac structure, with a bradycardia and occasional non-conducted atrial extra-systoles. The pattern appeared to be due to complete heart block.

Immunological assessment showed a raised C-reactive protein (10.1 mg/dl, normal range 0-0.8) but normal C3 (149 g/l, normal 65-190) and C4 (20 g/l, normal 15-50), rheumatoid factor titre was 1:1280, anti-nuclear antibody titre >1:1280, cardiolipin antibody 8 γ -phospholipid units/ml (normal <10), and anti-Ro (SS-A) and anti-La (SS-B) antibodies were present (not quantitated). There was no evidence of active lupus. Subsequent assessment of fetal well-being was complicated by the fact that cardiotocography was of little value other than to estimate the baseline fetal heart rate, there being little variability and no reactivity to fetal movements. Similarly, due to the prolonged 'run-off' time in diastole, the umbilical artery resistance index (RI) was artificially high, and thus of limited value. The umbilical artery RI (defined as $A-B/A$, where A = height of the systolic wave form and B = the height of the lowest point above the baseline) falls during pregnancy, and a raised value is thought to indicate placental pathology resulting in increased vascular resistance. With the prolonged diastole, the end diastolic flow is lower than it would be at a normal fetal heart rate, resulting in raised RI values. Daily biophysical scores were normal, and weekly measurements of fetal growth were satisfactory. The heart rate varied between 70 and 80 beats/min.

At 34 weeks gestation the patient suffered an antepartum haemorrhage and then went into labour; in view of this a caesarean section was performed. Initial attempts to insert a regional

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block failed, and attempted intubation at induction also failed due to limited opening of her mouth and difficulty with neck extension. Ventilation was conducted via a laryngeal mask, and she was delivered of a 1799 g baby boy. There were no operative complications.

At birth the baby had a complete heart block with a ventricular rate of 70–80/min. The baby required no additional treatment and was discharged from the special care unit after 21 days. The mother made an uneventful recovery.

Discussion

Overlap syndrome is a term used to describe diffuse connective tissue diseases (DCTDs) overlapping in their onset and clinical manifestations. The classic descriptions of systemic lupus erythematosus, progressive systemic sclerosis, dermatomyositis and rheumatoid arthritis are well known, although over periods of several years they may evolve features more commonly associated with another DCTD. The propensity for evolution and transition among DCTDs has been noted in about 25% of patients (Dubois 1984). Overlapping features may occur concurrently, but more commonly over time, one syndrome takes on the features of another (Bennett 1985). The patient described initially had a seronegative juvenile chronic arthritis, but then developed antibodies consistent with systemic lupus erythematosus (SLE), although there were no signs of active disease.

Congenital complete heart block was first recognized by Morquio (1910) and occurs about once in 20 000 births (Michaelson Engle 1972). The relation with maternal connective tissue disease has long been known (Hogg 1957); for example congenital complete heart block is the commonest manifestation of the neonatal lupus syndrome (Watson *et al.* 1984). It is a permanent defect, and occasionally requires pacing after birth. The evidence suggests that fetal myocarditis occurs, and is associated with scarring of the conduction system including fibrotic replacement of the sinoatrial and atrioventricular nodes, and calcification along the ventricular portions of the conducting system and the sinoatrial node (Carter *et al.* 1974; Litsey *et al.* 1985).

The fetal cardiac dysfunction usually appears in the second trimester of pregnancy (Scott *et al.* 1983; Singen *et al.* 1985) after the heart has

completed its main development. The defect is acquired, since normal heart rates and function have been observed before the development of complete heart block (Singen *et al.* 1985; Buyon *et al.* 1987). The myocardial lesion is, apparently, specific for the fetus, with no evident heart disease in the mother.

Most infants with congenital complete heart block are born of Ro (SS-A) antibody positive mothers (Scott *et al.* 1983; Reed *et al.* 1983; Lockshin *et al.* 1983), but sometimes only the La (SS-B) antibody has been detected (Weston *et al.* 1982; Buyon *et al.* 1987). Anti-Ro (SS-A) positive women whose infants are born with complete heart block have higher titres of anti-La antibody than those who have normal infants (Provost *et al.* 1987). This suggests a pathogenic role for the anti-La (SS-B) antibody.

Nevertheless, anti-Ro (SS-A) seems to be relevant in that the antibody reacts directly or indirectly with a cardiac antigen. The heart contains one of the highest concentrations of Ro (SS-A) antigen (Wolin & Steitz 1984; Harley *et al.* 1985), and IgG deposits have been found in the cardiac tissues of an affected infant (Litsey *et al.* 1985). The evidence suggests that a passively acquired autoantibody, probably anti-Ro (SS-A), binds to an autoantigen in the fetal heart and produces inflammation and fibrosis in the cardiac conduction system.

Because the heart conduction defects usually develop in the second trimester of pregnancy (Scott *et al.* 1983; Singen *et al.* 1985), at a time when there is increased transport of maternal antibodies across the placenta, treatment has been directed towards decreasing the quantity of maternal autoantibody, or to suppressing fetal myocarditis and specific inflammation of the conduction system. Plasmapheresis is unsuccessful in reversing established congenital heart block (Herreman & Galezewski 1985; Buyon *et al.* 1987), but may prevent myocarditis and limit cardiac damage. However, in those patients at high risk, thrice weekly plasmapheresis in conjunction with steroid therapy from 18 weeks gestation has been used with apparent success (Buyon *et al.* 1988). Steroids, prednisolone or dexamethasone, have been used in an attempt to suppress the fetal immune response and limit cardiac inflammation (Buyon *et al.* 1988; Buyon *et al.* 1987). Dexamethasone leads to higher steroid concentrations in the fetal circulation (Blandford & Murphy 1977) and is considered preferable to prednisolone, but prolonged

administration of high dose steroids may have side effects (diabetes, infection) in the mother (Fox & Hawkins 1990), may adversely affect fetal development and, if pacing of the heart is necessary after birth necessitating a surgical procedure, healing may be adversely affected.

The risk of having a child with complete heart block for a woman with anti-Ro (SS-A) antibodies and no previous children with heart block is reported to be 1:20 (Ramsey-Goldman *et al.* 1986), increasing to 1:3 after one affected child (Buyon *et al.* 1988; McCune *et al.* 1987). The presence of anti-Ro (SS-A) and anti-La (SS-B) antibodies thus has serious implications for future pregnancies. It is apparent that Still's disease or other connective tissue disorders in a pregnant woman cannot be considered to be completely innocuous, despite their inactivity; further, that a previously unaffected child does not preclude a later affected fetus. It is thus necessary to screen all such patients for anti-Ro (SS-A) and anti-La (SS-B) antibodies, and monitor appropriately if the antibodies are present.

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SHORT COMMUNICATIONS

Cervical preparation with gemeprost for dilatation and evacuation

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Dilatation of the pregnant cervix above 12 mm, for termination of pregnancy, has resulted in concern regarding the risk of trauma and subsequent cervical integrity (Johnstone *et al.* 1976; Obel 1979). In the USA, preoperative cervical dilatation using *Laminaria japonica* tents improves the ease and safety of operative termination (Grimes & Schulz 1985) but takes between 18 and 36 h (Castadot 1986). Gemeprost, a prostaglandin E₁ analogue, administered as a vaginal pessary, was found to be easier to administer and faster acting than Lamicel for adequate cervical preparation before first trimester dilatation and suction evacuation (Helm *et al.* 1988). We report our experience of the use of vaginal gemeprost for cervical preparation in 141 consecutive patients having second trimester dilatation and evacuation.

Methods and results

Initially, treatment was started the evening before morning surgery. The first 41 women had 1 mg and the subsequent 21 women had 0.5 mg gemeprost placed in the posterior fornix of the vagina. They were examined again 8-10 h later. The next 79 women were treated with 1 mg of

gemeprost in the morning before afternoon surgery and were examined again 3-6 h later. The need for a second dose was at the discretion of the examining doctor and, in general, reflected the opinion that further softening was required. At operation, under general anaesthesia, the cervix was dilated using Hawkin-Ambler tapered dilators. The aim was to achieve a dilatation, in millimetres, equal to the gestation in weeks, unless firm resistance occurred before this.

Twelve (8%) of the women aborted before planned surgery. Ten had been treated overnight (8 with 1 mg and 2 with 0.5 mg of gemeprost) and the interval from first dose to abortion (mean 11.9, SD 2.7 h) was similar to the interval from first dose to operation for the remaining 52 patients (mean 13.7, SD 1.6 h). However, the mean gestation of those who aborted (14.7, SD 1.0 weeks) was less than that of the other patients treated overnight (17.1, SD 2.2 weeks, $t=5.510$, $df=31$, $P<0.001$). Two of the eight women (both 14 weeks) had been given a second dose of 1 mg. Two multipara given gemeprost in the morning, one having a single dose (14 weeks gestation) and the other having a repeat dose 3 h later (18 weeks gestation), aborted after 9.5 and 9.0 h respectively. The mean interval from first dose to operation for the remaining 77 patients treated in the morning (5.0, SD 1.8 h) was much shorter than this and was significantly shorter than the mean overnight treatment interval ($t=28.2$, $df=127$, $P<0.0001$).

Overall, administration of two gemeprost pessaries increased with increasing gestation ($\chi^2=9.34$, $df=3$, $P<0.05$) and the mean gestation of those receiving two pessaries (17.0, SD 2.16 weeks) was significantly greater than that of those who received one pessary (15.7, SD 2.04 weeks, $t=3.50$, $df=125$, $P<0.001$). Although the ratio of nullipara to multipara (two to one) was similar in each gestation group a greater proportion of nullipara (48%) compared with multipara (18%) received two pessaries ($\chi^2=11.02$, $df=1$, $P<0.001$).

Mean age (22.5 years) and the proportion of nullipara (66%) were similar in the overnight and same-day groups. There were also no differences

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Table 1. Cervical dilatation for second trimester uterine evacuation after pretreatment with vaginal gemeprost pessaries.

Gestation (weeks)	Number <i>n</i> (%)	Cervical dilatation* (mm)	Treatment interval† (h)
		Median (range)	Median (range)
Overnight treatment			
12-14	10 (19)	14.0 (12.0-18.0)	14.0 (12.0-16.0)
15-16	12 (23)	16.0 (12.0-18.0)	12.5 (12.0-15.0)
17-18	16 (31)	18.0 (14.0-20.0)	14.3 (11.0-16.5)
19-21	14 (27)	20.0 (20.0-22.0)	14.0 (10.0-17.0)
Same-day treatment			
12-14	29 (58)	14.0 (10.0-17.0)	4.5 (2.0-7.0)
15-16	22 (29)	16.0 (12.0-19.0)	5.0 (2.0-8.0)
17-18	19 (24)	18.0 (16.0-21.0)	5.5 (2.0-8.0)
19-21	7 (9)	20.0 (16.0-21.0)	6.0 (4.0-8.5)

ANOVA for trends with gestation:

*Overnight group $F=39.45$, $df=3$, $P=0.0001$ Same-day group $F=29.30$, $df=3$, $P=0.0001$ †Overnight group $F=1.63$, $df=3$, $P=0.20$ Same-day group $F=2.50$, $df=3$, $P=0.07$.

in age or parity with increasing gestation. Table 1 shows that the treatment interval in the overnight group did not vary with gestation whereas there was a trend (not statistically significant) for the same-day group to have a longer interval as the gestation increased. The cervical dilatation achieved at operation equated significantly with gestation and was similar in each treatment group. Abdominal pain requiring analgesia was experienced by 24 (39%) of the overnight treatment group compared with 5 (6%) of the women treated in the morning ($\chi^2=22.3$, $df=1$, $P<0.0001$). There were no cervical lacerations, either during dilatation or evacuation. The uterus was perforated in one woman, attributed to manipulation of fetal parts within the cavity, and was repaired at laparotomy. The ectocervical epithelium was torn by the volsellum in three women (gestations 14, 14 and 16 weeks) during dilatation to 16, 13 and 18 mm after treatment in the morning with one pessary for 2, 3 and 4 h respectively. Only one of these required suturing for haemostasis.

Discussion

Dilatation and evacuation as a method for second trimester termination of pregnancy remains uncommon in the UK, accounting for approximately 4% of NHS and 20% of private late terminations (Stanwell-Smith 1984), despite the fact that it has been shown to be safer than instillation methods (Cadesky *et al.* 1981; Grimes & Schulz

1985). Early reports of the procedure indicated the need to dilate the cervix up to 20 mm (Slome 1972; Finks 1973).

Extensive dilatation of the cervix is necessary for the removal of large fetal parts. Cervical dilatation of the unprepared cervix for first trimester termination resulted in a wider residual dilatation which suggested damage to the structural integrity of the cervix (Johnstone *et al.* 1976). A significant increase in the rate of low birthweight babies was found to follow cervical dilatation over 12 mm compared with less than 12 mm (Obel 1979). Cervical incompetence and second trimester miscarriage have also been related to cervical dilatation (Grimes & Schulz 1985). Indeed cervical injury is one of the most frequent complications and the frequency of cervical lacerations requiring suturing may be as high as 1.2% (Grimes & Cates 1979).

We found that preoperative cervical preparation with gemeprost resulted in sufficient cervical softening for easy and adequate cervical dilatation, sometimes up to 22 mm, with no significant cervical trauma. Multipara and earlier gestation pregnancies were more likely to require only one pessary. Overnight preparation, especially with 1 mg, for a morning operating list was associated with a significant frequency of abdominal pain requiring analgesia and resulted in some complete abortions. Shorter, same-day, preparation for an afternoon operation list significantly reduced these problems and also allowed some patients to be managed as day-cases. Our

experience suggests that 5 h of vaginal gemeprost will achieve sufficient cervical preparation, with minimal discomfort and risk of abortion, for second trimester dilatation and evacuation up to 21 weeks gestation.

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Early endometrial carcinoma: an incidental finding after endometrial resection. Case report

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Case report

A 38-year-old woman was referred with a 4-year history of menorrhagia. Her menstrual cycle had always been regular except for two episodes in the last 6 months. Her measured menstrual blood loss using the alkaline haematin method of extraction was 90 ml. She had had two children and her husband had subsequently had a vasectomy. She weighed 82 kg (body mass

index = 36.4, height/weight²) and had type 2 diabetes which had been controlled on glibenclamide 10 mg daily for 10 years. Hysteroscopy and dilatation and curettage showed a normal endometrial cavity and normal secretory phase curettings. Over the next 3 months her menses remained heavy but her cycle was regular. She agreed to participate in our randomized controlled trial of endometrial resection vs hysterectomy and was randomized to the former operation. Hysteroscopy again showed a normal cavity with secretory endometrium and a complete resection was performed with removal of uterine strips weighing a total of 10 g. Histological examination showed moderately differentiated adenocarcinoma present in 5 of 7 strips. The areas of carcinoma appeared alongside both secretory and hyperplastic endometrium. There was no myometrial involvement. Four weeks later abdominal hysterectomy with conservation of ovaries was performed. Histological examination showed the cavity to be lined with granulation tissue but there was no residual carcinoma.

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Discussion

Endometrial carcinoma is rare in women under 40 years of age accounting for only 5% of the cases (Peterson 1968). Obesity occurs in 80% of these young women and is the most significant clinical finding in patients with this disease. The incidence of diabetes mellitus is 20%, and 65% of patients can be expected to have a long history of menorrhagia and menstrual irregularity. For many reasons, therefore, our patient was in a high risk group. Traditionally, curettage is used to diagnose intrauterine abnormality (Mackenzie & Bibby 1978) although hysteroscopy and directed biopsy are now commonly used (Gimpelson & Rappold 1988). It is disturbing that both these procedures failed to identify the abnormality although changes were restricted to within the endometrium on histological examination and no biopsy was taken under direct vision using the hysteroscope as has been reported successfully (Raju & Taylor 1986). A 10% rate of missed endometrial lesions has been reported after curettage (Word *et al.* 1958) and, in another study where hysterectomy specimens were examined after a preoperative curettage, 60% had at least half the cavity uncuretted (Stock & Kanbour 1975). Perhaps outpatient biopsy using a resectoscope to obtain a full thickness endometrial strip should be considered in high risk groups. The

importance of the histology after endometrial resection emphasizes its advantage over laser ablation (Davis 1989) as a minimally invasive technique for the treatment of dysfunctional uterine bleeding.

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Use of intra myometrial 15-methyl prostaglandin $F_{2\alpha}$ to control atonic postpartum haemorrhage following vaginal delivery and failure of conventional therapy

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15-methyl prostaglandin $F_{2\alpha}$ (15m-PGF $_{2\alpha}$) (Hemabate, Carboprost, Upjohn Limited) is licensed in the United Kingdom for intramuscular administration to control atonic post-partum haemorrhage where conventional therapy has failed. By this route, the maximum effect may not be seen until 45 min after administration (Hayashi 1990). Speed of action is essential with atonic uterine haemorrhage and if 15m-PGF $_{2\alpha}$ is given intramyometrially, the onset of action is within 5 min in most patients. We describe 14 women treated with intramyometrial 15m-PGF $_{2\alpha}$ where atonic haemorrhage had continued unabated after conventional therapy.

Correspondence: Mr M. D. Read

Table 1. Details of 14 patients with atonic postpartum haemorrhage.

Patient no	Parity	Mode of delivery	Estimated blood loss (l)	Delivery to EUA (h)	Units transfused	Drop in Hb at 48 h postpartum (g/dl)	Complications
1 + PH	2	NVD	2.8	2 GR	4	1.8	None
2 + H	0	V	3.0	1 G	6	0.4	Pyrexia 38.5°C for 2 h
3 +	2	NVD	1.5	3 G	2	4.5	None
4 +	0	V	1.0	11 G	2	2.7	None
5 +	0	V	2.5	4 GR	4	3.5	Tachycardia for 48 h
6 +	2	NVD	4.0	2 G	8	2.4	Unsuspected coagulopathy
7 + H	0	NVD	1.0	1.5 G	3	6.2	None
8 + H	1	V	1.7	5.5 G	2	3.8	Tachycardia for 24 h
9	1	NVD	1.1	1.5 GR	2	1.3	None
10	0	V	1.7	1.5 S	2	2.2	Pyrexia 38.0°C for 24 h
11	0	LCF	1.0	1 E	0	3.6	Vomiting
12 PH	2	NVD	2.5	2 SR	4	2.3	None
13	0	NVD	1.0	1	0	2.1	Headache & vomiting
14	0	V × 2	1.2	7 G	0	2.6	(Twin pregnancy) none

Abbreviations: H = pre-existing hypertension; P = previous PPH; V = Ventouse, R = Retained placental tissue present at EVA, E = Epidural; EUA = Evacuation of uterus; + Induced labour with PGE₂ gel; NVD = Normal vaginal delivery; LCF = Low cavity forceps; S = Spinal anaesthesia; G = General anaesthesia.

Subjects and method

Table 1 gives the details of the 14 patients. They were between 39 and 42 weeks gestation. All the patients were examined under general or spinal anaesthesia and the uterus was evacuated where appropriate before administration of the 15m-PGF₂α. All women had been given Syntometrine (1 ml) intramuscularly at the time of delivery as a prophylactic measure, except those with pre-existing hypertension who were given 10 units of oxytocin intramuscularly. When the atonic haemorrhage was diagnosed, all the women were given a therapeutic injection of 500 µg of ergometrine intravenously and oxytocin (80 U/l) was infused at a rate of 120 ml/h. Resuscitation measures were commenced with intravenous plasma volume expanders and blood transfusion where necessary. Following exploration of the uterus, the intravenous infusion of oxytocin was continued and in all 14 women bleeding continued unabated with the uterus relaxed and showing no signs of sustained contraction. A solution of 15m-PGF₂α (250 µg in 5 ml of normal saline) was injected transabdominally into the fundus of the uterus using a 20 gauge spinal needle. The syringe was aspirated before injection to avoid intravascular injection and resistance on injection confirmed that the needle tip was within the myometrium rather than in the uterine cavity.

Results

Intra-myometrial 15m-PGF₂α arrested serious haemorrhage promptly in 13 out of 14 women. Response was poor in the remaining woman because of an unsuspected coagulopathy. Two patients received a second injection, one of them (no. 3) had a good response to the injection in theatre but the uterus became atonic and started to bleed again 1 h later. A second injection was given in the recovery room and no further problem occurred. The second woman (no. 2) was given two injections in theatre because of the profuse nature of the haemorrhage. The response was excellent. Following recovery from the general anaesthesia she required persistent ventilation for 10 min and was rather confused with laboured breathing, for which she received midazolam. She was also hypertensive, with a blood pressure of 180/110 mmHg, which responded to intravenous hydralazine (she had hypertension before induction of labour, but the highest record of blood pressure before this episode was 90 mmHg diastolic). She also developed a transient pyrexia of 38.5 which lasted for 2 h. One other patient developed a significant side effect with a pyrexia of 38° which lasted 24 h. No focus of sepsis could be found in either patient. Mild nausea was common and occurred in nine women, seven of whom had had a general anaesthetic and two a spinal.

Conclusion

These data are uncontrolled and it is easy to give credit for the arrest of haemorrhage to the last therapeutic agent given. However, intramyometrial 15m-PGF₂α appears to be extremely effective in arresting serious atonic haemorrhage. Important but self-limiting side effects are seen. We conclude that 15m-PGF₂α should be used with careful supervision by experienced obstetricians, and urge that all delivery units should have a supply immediately available. Since the intro-

duction of 15m-PGF₂α in our hospital, no woman has required a hysterectomy for an atonic post-partum haemorrhage.

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CORRESPONDENCE

Fish-oil and pre-eclampsia

Dear Sir,

In their recent commentary 'Fish oil and pre-eclampsia' [*Br J Obstet Gynaecol* (1990) 97, 1077-1079] Doctors Secher and Olsen advocate the organization 'as soon as possible' of large, controlled multicentre trials to assess the effects of fish-oil supplementation in pregnancy. One potential complication of such supplementation is a significantly increased bleeding time, such as has in fact been reported both in rats (Begent *et al.* 1984) and man following ingestion of diets rich in n-3 fatty acids (Goodnight *et al.* 1981; Lorenz *et al.* 1983; Mortensen *et al.* 1983). However, there are at least three other areas of potential concern, relevant to pregnancy.

Where detailed studies of the effect of a high fish-oil intake in man have included information on platelet counts, several have described an overall fall, ranging from 4 to 35%, the larger of which have been statistically significant (Goodnight *et al.* 1981; Hay *et al.* 1982; Lorenz *et al.* 1983; Mortensen *et al.* 1983). Indeed, in one apparently normal volunteer, frank thrombocytopenia developed after 3 weeks (Goodnight *et al.* 1981). A falling platelet count is seen in association with worsening pregnancy-induced hypertension (PIH); it would appear to be unwise to risk magnifying such a fall. However, Starling and his colleagues, in small-scale pilot studies of Maxepa and Himega for the prevention of PIH, have so far found no consistent change in platelet count during treatment (Dr M. B. Starling, personal communication).

Serum uric acid concentrations are rarely reported in such studies, but there is one report in which they are considered, in which an increase in serum uric acid, of up to 24% after 2 weeks treatment, occurred (Singer *et al.* 1985). A rise in serum uric acid is also found in association with worsening PIH, so that another confounding factor could be introduced.

Dr Olsen's own work has suggested a prolongation of gestation in Faroese women who eat a high proportion of 'marine victuals' by compari-

son with the otherwise very similar Danish women (Hansen & Olsen 1988). This is in agreement with studies on pregnant rats (Leat & Northrop 1979; Leaver *et al.* 1986) in which prolonged labours were also reported. This could be suggested as being due to a shift of production away from the potent 2 series prostanoids concerned with uterine contractility, and might have implications where the induction of labour is indicated.

There is very strong evidence to suggest an imbalance in production of vasodilator, antiaggregatory/vasoconstrictor, proaggregatory eicosanoids in hypertensive pregnancy. The possible use of dietary supplementation to redress such an imbalance is most attractive, and is likely to be acceptable to many women perceiving it being 'natural'. This should not blind us to the possibilities of adverse side-effects, which might go unreported for some time in large-scale clinical trials. Very carefully-monitored trials in centres with direct interests in the field of fatty acid research might be a more appropriate approach to begin with.

F. Broughton Pipkin

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Dear Sir,

Your recent editorial (Secher & Olsen, 1990) highlighted the possible benefits of fish oil supplementation during pregnancy. Studies which have reported a reduction in preterm delivery and pre-eclampsia did not involve ingestion of a fish oil preparation, but rather a diet rich in n-3 fatty acids.

Choice of preparation is important, as recently concern has been expressed regarding the possibility of vitamin A overdose in pregnant women taking fish oils and of vitamin A teratogenicity (Yetiv 1988; Nelson 1990). Maxepa fish oil, which contains a negligible amount of vitamin A may therefore be appropriate, and

has been reported to achieve beneficial effects on prostaglandin metabolism with doses of up to 50 ml daily. Limited attention has been paid to patient acceptability at these doses. Ingestion was quoted as 'tolerable' in one study (Knapp & Fitzgerald 1989), whilst in another at a dose of 16.5 g daily, 13 out of 16 patients were said to have preferred the oil to their previous treatment (Norris *et al.* 1986).

We assessed the response of 10 pregnant volunteers to the ingestion of 10–20 ml Maxepa prior to investigating the effect of fish oil on prostaglandin metabolism in pregnancy. All patients described the preparation as unpleasant, and because of the taste most of them were not prepared to take a further dose.

The suggested doses used in previous trials amounts to large volumes, or up to 50 capsules daily. In our experience, this preparation in its current form, even when mixed with fruit juice as suggested by the manufacturers is not a practical or acceptable treatment for most pregnant patients. Belching and unpleasant taste are the most frequently reported side effects with fish oil supplements (Secher & Olsen 1990), and these cannot be described as 'trivial' if they significantly reduce patient compliance.

We feel the possible benefits of fish oil supplementation in pregnancy will not be fully realised until attention is given to synthesis of a more concentrated and palatable preparation. Since similar beneficial effects have been reported with low dose aspirin therapy in pregnancy, it would appear that this may be a more appropriate form of treatment.

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Author's reply

We thank Dr Fiona Broughton Pipkin for raising some important issues relating to our suggestion of a multicentre trial of fish oil in pregnancy. We agree completely with her about the need for carefully-monitored trials in this field. Indeed, before launching our multicentre trial, we randomized 535 women in the 30th week of gestation to fish oil (2.8 g n-3 fatty acids per day), olive oil or no supplement. Preliminary analyses have shown that the fish oil group had no increased occurrences of prolonged labour,

induced deliveries or bleeding complications. A subgroup was followed closely with blood and urinary samples. The trial groups had similar serum uric acid and coagulation factors. In particular, the difference between PAI-1 in serum and PAI-1 in plasma, which is held to reflect platelet reactivity, was similar; we did not perform platelet counts. The results mentioned are preliminary, and final results from the trial will be published in due course.

We do not agree that the decision to undertake a multicentre trial should depend crucially on the findings from 'very carefully-monitored trials', since such trials are bound to have low statistical power to detect even substantial increases in the occurrence of rare complications, and because paraclinical findings are likely not to be of much help in the decision process. As pointed out by Dr Broughton Pipkin, it is well established from studies in non-pregnant subjects that fish-oil prolongs bleeding time and, somewhat less well established, that it reduces the platelet count. Nevertheless, to our knowledge none of the numerous randomized trials with fish oil in non-pregnant subjects (often employing much higher doses than in our study) has shown clinically detectable complications related to an increased bleeding tendency. So, even if a prolongation of bleeding time and a moderate reduction in platelet count were seen after fish oil also in pregnant women, we would not, from these findings alone, expect that fish oil also increases the risk of bleeding complications in pregnant women. Consequently we feel that undertaking a trial to assess whether fish oil has any prophylactic or therapeutic effects on pre-eclampsia, fetal growth retardation and pre-term delivery, would be justified irrespective of such paraclinical findings. We are carefully monitoring the multicentre trial for bleeding complications, and we exclude patients with previous abortion or severe bleeding in the actual pregnancy.

Dr Broughton Pipkin mentions the possibility of worsening a pre-eclampsia-induced thrombocytopenia with fish oil. The thrombocytopenia seen in severe pre-eclampsia and the fish-oil-induced reduction in platelet count are believed to have quite different mechanisms, the first via an increase in platelet aggregation, the second probably via a decrease in platelet production (Hay *et al.* 1982). In theory, a lowering in platelet production could aggravate the risk of maternal bleeding, a serious complication of the

DIC-syndrome, but it could also reduce the tendency of disseminated coagulation and thereby avoid further the impairment of placental blood flow which is threatening the fetus. However, due to the small theoretical possibility that fish oil could aggravate the risk of bleeding in severe pre-eclampsia, we enjoin great caution in our trial in such cases. We do not think, however, that these worries are a contraindication to undertaking a multicentre trial with fish oil in pregnancy.

We mentioned in our commentary that it is our impression that fish oil is increasingly being used by the general population of pregnant women. It may therefore be unwise, and even unethical, to wait until the widespread use of fish oil has made it impossible to undertake a carefully controlled trial assessing the possible beneficial as well as any deleterious effects that fish oil may have in pregnancy.

We take the opportunity to direct the attention towards a recent report that rats receiving standard rat chow supplemented with fish oil had longer gestation than when the standard rat chow was supplemented with arachis oil (Olsen *et al.* 1990). This is a finding that is quite different from the rat studies cited by Dr Broughton Pipkin (Leat & Northrop 1979; Leaver *et al.* 1986) where fish oil in both cases was supplemented to a linoleate-deficient-diet, and where the prolonged gestation could be due to the n-3 fatty acids added as well as to the (absolute) lack of n-6 fatty acids (indeed, the latter may well explain their findings of prolonged labour).

Dr McCormack and Dr Constantine are right, we feel, in recommending fish oil with low amount of vitamin A to pregnant women, and also that the preparation should be as concentrated as possible with n-3 fatty acids to keep the volume to be ingested at a minimum. In the trial mentioned above we used Pikasol fish oil which, like Maxepa, contains negligible amounts of vitamin A but which has an n-3 fatty acid content of 60–70%. Contrary to McCormack and Constantine's experience, ours was that there was a relatively good compliance, with about 75% of the 269 women adhering to our prescription to take four 1 g fish oil capsules per day (assessed by a questionnaire after delivery). Among those receiving fish oil capsules, 23% reported pronounced belching and 16% unpleasant taste, compared with 8.5% and 2.3% respectively among those receiving olive oil capsules, while the occurrences of nausea, vomiting, stomach

ache and diarrhoea were low and quite similar in both groups.

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The use of cervicography in a primary screening service

Dear Sir,
I am confused by the results presented in the paper by Szarewski *et al*. [*Br J Obstet Gynaecol* (1991) 98, 313-317] and have attempted to construct the usual 2 × 2 table used to analyse data of this sort.

Total number of women with a positive test result

In the third paragraph of the Results the authors say 'A total of 112 women had biopsies as a result of a positive cervicogram' and 'There were also 13 women in whom a positive cervicogram was followed by negative colposcopy and no biopsy was taken'. This suggests that a total of 125 women were referred for colposcopy because of a positive cervicogram.

However, in Table 2 the authors state that 130 women had colposcopy and biopsy, 19 had colposcopy which was negative and no biopsy was taken, and six had colposcopy advised but the results were not traced. This would suggest that there were 155 women with a positive cervicogram.

These figures in turn do not match up with the numbers shown in Table 1 where 150 patients would have been referred for colposcopy on the basis of a positive cervicogram as defined by the authors (one that indicated HPV or any degree of CIN or cancer). I have chosen to use this number in the table.

The number of women with positive tests and confirmed CIN/HPV.

Table 3 suggests that 93 women had histologically diagnosed HPV/CIN I or CIN II or worse following a positive cervicogram.

The number of women with negative tests but confirmed CIN/HPV.

In the fourth paragraph of the results the authors state that 16 of the concurrent smears were positive. In three of these women the biopsy was negative. Thus 13 had positive biopsies and we are left to assume that the cervicography was negative.

The total number of women from whom data are available

Results of colposcopy could not be traced for six patients and 113 women had defective cervicograms. This leaves data from 1044 women for analysis.

Using the figures derived above the following table can be constructed:

Test result	Disease status		Total
	Present	Absent	
Positive	93	57	150
Negative	13	881	894
Total	106	938	1044

Definition of terms used (Brown & Swanson-Beck 1989)

The sensitivity of a test is defined as the proportion of the patients who have the disease in whom the test result is positive. The specificity is the proportion of healthy subjects in whom the test is negative. The false positive rate is the proportion of the healthy subjects who give a positive test result and the false negative rate is the proportion of those subjects who have the

disease but who give a negative test result (Morton & Hebel 1984; Brown & Swanson-Beck 1989). Note that in these definitions, the number of subjects with or without disease form the denominators.

It should be noted that this definition of the false positive rate differs from that used by the authors. It would seem that what the authors are referring to is the inverse of the positive predictive value of the test, the positive predictive value being the probability that disease will be found in a woman who has a positive test result. In this definition, the number of subjects with a positive test result is the denominator.

Results of the study

Provided the table does accurately reflect the authors' results (and it is difficult to be sure that it does) the sensitivity of cervicography was 88% (93/106) and specificity was 93% (881/938). The inverse of the positive predictive value which the authors refer to as 'the false positive rate' was 38% (57/150).

Comment

It would have been of interest to know what the yield of pathology was from the 1007 routine smears taken from women who attended before March 1988. In particular, as the authors have focused upon the positive predictive value, this statistic for the cytology would have been helpful to put the cervicography results in context.

Evaluating diagnostic or screening tests is difficult enough at the best of times but it seems particularly regrettable that the authors of this paper should have chosen not to present their data in a more clear cut and easily understood way and that they should have used the terminology in this unusual fashion.

W. P. Soutter

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Dear Sir,

In their study of the use of cervicography in primary screening for disease of the cervix, Szarewski *et al.* [*Br J Obstet Gynaecol* (1991) **98**, 313-317] greatly underestimate the false positive

rate for cervicography and fail to make a valid comparison between cervicography and cervical cytology.

Their classification of positive biopsies combines cases showing CIN I together with those showing only changes of HPV infection. This large group accounts for 60% of all their biopsies and will include not only biopsies showing mild dysplasia, but also those in which there may be only minor degrees of koilocytosis. It is inappropriate to regard all of these cases as true positives.

Their criteria for a positive cervicograph, which include those showing evidence of HPV infection alone, are not comparable to the ambiguous criteria they use to define a positive smear. They define a positive smear as one which led to a recommendation for colposcopy but also say that smears were considered positive if they showed any dyskaryosis. In most laboratories smears showing only mild dyskaryosis do not lead to a recommendation for colposcopy but for early follow-up. The rate of progression of cervical disease is such that a policy of limiting colposcopy and biopsy to higher grade lesions or persistent abnormalities is a safe one. As it is not clear what Szarewski *et al.*, mean by a positive smear it is difficult to comment on their figure of 1% positivity for routine cytology, but this figure is vastly lower than the rate of detection of abnormalities is most laboratories.

This report has not demonstrated that cervicography is of any value in detecting significant lesions in women with normal smears but it may have caused some alarm amongst them. If anything, this report reinforces the suspicion that use of cervicography would result in huge over-investigation without any improvement in the detection of significant disease.

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Authors' reply

Dear Sir,

Mr Soutter is unclear about the number of women with positive test results and the numbers in his table are incorrect. Our Table 1

shows the cervicography results of all the women seen, whereas Table 2 gives the subsequent action, which did not necessarily always follow the recommendations because of doctor and patient choice. In particular, 19 women with cervicography results suggesting either HPV or CIN 1 are included in the 'no colposcopy' group. In 13 of these a decision was made to manage them by cytology. The remaining six were either still awaiting colposcopy, or the biopsy results were not available at the date on which the study was terminated. Of these six, we have subsequently found that one had a biopsy showing HPV, three had negative biopsies and two moved away and have not yet been traced.

Also, as noted in the paper, 24 women had colposcopy (six without biopsy), although referral was not recommended on the basis of cervicography or cytology.

Number of women with negative cervicograms but confirmed CIN/HPV

The remainder of the paragraph to which Mr Soutter refers makes it clear that in only three cases where the smear was positive was the cervicogram negative: in one of those the biopsy report was also negative, and in a second, the report requested a brush smear. In both cases with a positive biopsy, the report was of CIN 1/HPV.

Definition of terms used

Because patients with negative cervicograms and smears were not colposcoped, it is not possible to discuss the sensitivity of the test. This is a common circumstance in large screening programmes, and under these conditions, it is generally accepted that the false positive rate *for the test*, defined as the number of patients judged

positive who were found to be negative on further investigation, is a useful measure for describing the performance of a screening test (Altman, 1991; Gastwirth 1987).

Drs Rubin & Kocjan were concerned about the criteria used to define positive cervicograms, smears and biopsies. We chose to report the results in accordance with NTL's recommendations for cervicograms and the clinic's policy for referrals as a result of cytology. The decision to call biopsies showing HPV or CIN 1 positive is common in the literature (Giles *et al.* 1989). There is currently much controversy about the natural history of mild cervical lesions and opinion is divided as to how these should be managed. The criteria used in a private clinic are likely to be different from those which would be applicable in a national screening programme. In order to facilitate an assessment using other criteria, we have tabulated the results according to severity of cervicography and biopsy categories (Table 1).

Positivity rates for cytology

Contrary to Drs Rubin and Kocjan's claim, our criteria for a positive smear were clearly given in the paper (Results para 2 and were 'any degree of dyskaryosis', which, at the Marie Stopes Clinic, 'leads to a recommendation for colposcopy'.

The low positivity rates for cytology in the reference group probably reflect the result of clinic policy, which recommends annual smears and refers all women with abnormal smears (of any grade of dyskaryosis) for colposcopy. We believe that women coming for cervicography would also have been managed by this policy in the past. Our purpose in presenting these data

Table 1. Results according to severity of cervicography and biopsy categories

Cervicogram results	Colposcopy and biopsy results						Total
	Neg colp, no biopsy	Negative biopsy	HPV biopsy	CIN 1 biopsy	CIN 2 biopsy	CIN 3 biopsy	
HPV	2	2	10	3	0	2	19
CIN 1	8	14	23	16	10	2	73
CIN 2	3	2	3	6	2	4	20
CIN 3	0	1	2	2	1	3	9
Micro invasion/ invasion	0	0	2	0	0	2	4
Total	15	19	40	27	13	13	125

was not to recommend cervicography for a national screening programme, but simply to point out potential advantages and disadvantages of the method at its current stage of development. The very high detection rate means that many small and possibly insignificant (CIN1/HPV) lesions are detected and referred for colposcopy. We hope that future research and development will be undertaken to address this problem, and also to determine the optimum role for the test. For example, it may have a better use in second line screening of women with a mildly abnormal smear, since up to 49% may actually have higher grade disease on colposcopy and histology (Soutter *et al.*, 1986).

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BOOK REVIEWS

Textbook of Fetal and Perinatal Pathology, Volumes I & II, edited by Jonathan S. Wigglesworth and Don B. Singer. Blackwell Scientific Publications, Oxford 1990, Volume I 640 pages and Volume II 643-1038 pages, fully illustrated, £195. After many years of famine, it is a pleasure to find a sharp increase in the numbers of excellent paediatric pathology books. Over the last two or three years there have been several covering this whole age range of paediatric pathology. This book is exclusively about fetal and perinatal pathology. The publication is timely, as fetal medicine and early ultrasound diagnosis are expanding and developing very rapidly.

There are two volumes, the first of which deals with principles and major problems; the second with straightforward organ systems pathology.

The first volume starts with accounts of the role of the perinatal pathologist, normal growth values, classification of causes of death, and how to do a perinatal autopsy. These chapters set the tone of the book. I enjoyed reading the excellent prose and thoughtful, sequential problem solving approach which starts out with clear expositions of the basic data and leads the reader in gentle stages to a deep level of analysis. The rest of the chapters in this first volume are concerned with disorders of the fetus, placenta, stillborn, and neonatal death. Individual chapters on fetal death and the macerated stillborn fetus, chromosome abnormalities, dysmorphism, and causes of malformations are welcome, especially when, as here they are well written by thoughtful and knowledgeable experts. This volume fulfils the editors' stated objective of compiling a book which is equally useful for all professionals concerned with the care of the fetus and newborn infant. The multi-disciplinary problem solving approach they have adopted should make this part attractive to the wider readership.

The second volume adopts the more traditional system-based approach to disease which of necessity involves some repetition and to-ing and fro-ing through the book, as many diseases are multi-system. This is dependent on good internal cross-referencing, and I am delighted to

say that the editors have done a sterling job. After much searching I only found one possible error!

As well as the standard organ system chapters there are two chapters on topics not usually found in paediatric pathology books. These welcome additions are chapters on the eye, and the oro-facial region.

The chapters on the organ systems have, perhaps, a more restricted appeal that is largely to morbid anatomists. Within these limits, where the reader perhaps knows 50% of the answer, there are many outstanding chapters. The overall quality of all the chapters is high, but some chapters stand head and shoulders above other publications on the same subjects.

How pleasing to see an outstanding chapter on that most neglected of organs, the pancreas. The chapters on endocrine organs, and on the liver, provide informative, clear accounts of complex and puzzling topics. The cardiovascular section is useful. This does not go into great depths over rare conditions, but gives an excellent account of advanced examination techniques and classification. The chapter on the central nervous system is first class.

The most disappointing chapter is that on the skeletal system. The disappointment is not on the quality nor depth of information, which is outstanding, but on the photomicrographs and radiographs. Throughout the book the overall quality of photomicrographs both in composition and reproduction is excellent, which makes this chapter stand out in contrast. I have as much difficulty with radiographs as clinicians have with microphotographs, and I found some of both of them unclear.

Most contentious subjects are well handled, with suitable qualification and an almost encyclopaedic reference list. There is only the most occasional hint of over emphasis of one particular point of view, in most instances a very open statement of current thought is made.

The editors should be congratulated on their efforts in gathering together such an excellent group of authors, and producing an authorita-

tive work of reference which will also be very useful as an advanced laboratory handbook. Not the least of their achievements is to provide a depth of information throughout, yet to keep the whole book eminently readable. It is the best book yet in its field and should be available for all in the fields of fetal and perinatal medicine.

D. G. Fagin

Physiotherapy in Obstetrics & Gynaecology, by Margaret Polden & Jill Mantle. Butterworth Heinemann, Oxford/London, 1990, 441 pages, £28.95

The physician whose pre-registration house job I did taught me that 'physiotherapy is an unscientific discipline with no controlled clinical trials to prove or disprove its use'. It is with the memory of these pearls of wisdom that I read *Physiotherapy in Obstetrics and Gynaecology*. I was unaware that there is now an Association of Chartered Physiotherapists in O & G: sub-specialization marches on.

The book begins with a glowing forward to the book by Dame Josephine Barnes, herself one who has in the past demonstrated her adherence to the scientific method for resolving the effectiveness of clinical treatments.

There are accurately-illustrated and written chapters on female anatomy and physiology of pregnancy but it is regrettable that the authors still talk about 'toxaemia' of pregnancy (page 40). The physical and physiological changes in labour and the puerperium are well written but on page 73 they mention a paper by Grant (1987) which showed that polyglycolic ester sutures were the best material to sew up episiotomies, but failed to list this excellent work in the references at the end of the chapter. However in their defence other controlled trials on the use of birthrooms and squatting in labour are quoted and referenced.

I am unsure, reading *The Antenatal Period* what role physiotherapists have during this time because there is much discussion on diet, breast-feeding and weight gain. Are these not the provinces of the midwife, and dare I say it, the obstetrician as well? Is it correct that the physios should take over antenatal classes and teaching of such details as transcutaneous nerve stimulation? Do physiotherapists actually know how to stop the nausea and vomiting of pregnancy (page 123 and 159)? Better help is offered in the chapter on Relieving Pregnancy Discomfort, although all these treatments would have had

more respect from me if they had been subjected to the scrutiny of controlled trials. When acupuncture is mentioned I begin to put on my prejudicial hat. Although in my youth physios helped me with my libido, can physiotherapists really help the pregnant with theirs (page 245)? In this same chapter the excellent trial, again by Grant *et al.* (1989) on Electromagnetic Energy Treatment for Perineal Trauma' is dismissed by the statement 'Attempts to show that ultrasound or pulsed electromagnetic energy increased the rate of healing in the traumatized perineum have been disappointing'—why not say it doesn't work?

In the gynaecology section of the *Climacteric* it seems a pity that expensively-trained paramedicals are needed to advise premenopausal women that they should take more exercise and smoke less. One wonders if the country would benefit from taking physios out of hospitals and putting them in our schools to give this advice.

In the surgical section it states 'it is usual for women to be admitted at least (!) one day before major abdominal surgery'. If, however they were admitted on the same day they would be less likely to develop deep vein thrombosis (DVT) and therefore would not need physiotherapists to exercise their patients' legs after the operation. Have there been any trials of prevention of DVT using physiotherapy alone?

This is an interesting book which is well-written, but I feel it has a limited place in any gynaecologist's library, but could be usefully read, together with this review, by all physiotherapists.

John McGarry

Introduction to Clinical Gynaecological Urology by John R. Sutherst, Malcolm I. Frazer, David H. Richmond & Bernard H. Haylen. Butterworth-Heinemann, London 1990. 170 pages, with figures and tables, £19.95

This is an excellent book and the only one of its kind available. Divided into three sections, the text really does achieve what the title suggests and that is cover basic clinical urogynaecology. The first part of the book is devoted to the problem of incontinence followed by the anatomy, physiology and pharmacology of the lower urinary tract and finally the mechanism of the lower urinary tract and the mechanism of continence and causes of incontinence. The second section is devoted to investigations, starting with basic clinical presentation, then describing briefly the

simple non-invasive investigations followed by increasingly complex invasive tests and, lastly, those that are reserved for the investigation of difficult cases. The third section of the book is devoted to clinical management. There are large chapters describing the treatment of genuine stress incontinence and detrusor instability, the two most common causes of urinary incontinence in women, and then shorter sections to describe the treatment of voiding disorders and sensory disorders of the bladder and urethra. The last chapter describes the pads, pants and collection devices that are currently available to deal with intractable incontinence.

Clinical Gynaecological Urology is well written in a fairly didactic but easily digestible style. The book has plenty of simple line drawings, which are easy to understand, and is not overloaded with references, although there are suggestions for further reading at the end of each chapter. There is no doubt that this book is a must for every medical library and I am sure that it will be appreciated by all junior hospital doctors who are required to deal with women with lower urinary tract disorders. In addition I think that interested general practitioners would find much of the text useful and I am sure that nurses with an interest in gynaecology or urology will welcome this book as nothing has been written to equal it either by doctors or nurses. At £19.95 the book is not overpriced, the print is good and easy to read and it has been well produced. I will certainly recommend Clinical Gynaecological Urology to the many people who have asked me for a simple book on this complicated subject.

Linda Cardozo

CRC Handbook of Laboratory Diagnosis and Treatment of Infertility, Edited by Brooks A. Keel & Bobby W. Webster. CRC Press, Boca Raton, 1990, 431 pages, with figures and tables, £78.00

The stated aim of this manual is to provide clinicians and technicians diagnosing and treating infertile couples with a comprehensive, detailed and step-by-step handbook. The editors have, in most respects, succeeded in this aim. This is one of the most comprehensive manuals of its kind available.

In this book of 371 pages, 233 are devoted entirely to every aspect of semenology. This emphasis on sperm and sperm function causes a lack of balance in this volume. No room at all is given for example, to the endocrine investiga-

tion of infertile couples. There is only a chapter on the statistical methods for hormone assays—not a useful chapter for the practical management of couples. The chapter on the organization of the in-vitro fertilization and embryo transfer laboratory is very good and would be most helpful to any group wishing to set up such a facility. Protocols for all the procedures are very detailed and clear.

One of the many penalties of multiple authorship, even with the best editorial intention and attention, is gross differences in style and variations in the levels at which different authors aim their chapters and a tendency of subject matter to be repeated in different chapters. All of these problems arise in this book. The chapter on semen analysis by the senior editor is excellent, with just enough detail of the special tests available and their significance for most clinicians and scientists working in the field to gain practical knowledge. The effect is somewhat spoilt, however, by the concluding comment of the chapter that '... semen analysis is perhaps the most important test in the diagnosis of male infertility ...'. The inclusion of 'perhaps' in this statement rather undermines the authority of a very good chapter. The chapter on sperm washing and concentration techniques and the methods of sperm enrichment for X or Y bearing spermatozoa is most useful. It is surprising however that no mention is made of the more specialized methods of sperm preparation for more severe forms of oligospermia and asthenospermia for assisted conception, such as the use of discontinuous Percoll gradients or layering under paraffin.

Finally, the chapter on the cryopreservation of human semen is excellent, with good clear instructions and diagrams. It ends with authoritative guidelines on standards and regulation on cryostorage of sperm.

This handbook almost achieves its stated aims. It is very comprehensive but with an excessive emphasis on seminology, with endocrinology and certain other aspects of the investigation of the female partner being completely sacrificed. Nevertheless, this volume should be given a place on the library shelves of every unit involved in setting up assisted conception, both for its comprehensiveness in many parts of this specialty and for its very useful appendix and extensive references.

Peter Brinsden

Atlas of Ultrasound Measurements, Edited by

Barry B. Goldberg & Alfred B. Kurtz. Year Book Medical Publishers Inc., Chicago, London, Boca Raton, 1990, 462 pages, illustrated, £68.00

This is a highly comprehensive review of the technique and evaluation of ultrasound measurements with a little over half the book being dedicated to obstetrics and gynaecology. The preface explains that the book developed from specific questions raised by students attending ultrasound courses run by the authors. The commonest difficulty related to the plethora of published tables of 'standard' measurements. These are confusing for most of us and the authors attempt to provide a guide through this particular minefield.

The text is immensely detailed and not particularly fun to read. It does however, provide the academic ultrasonographer with a large bibliography, although the term 'recent study', which is used fairly commonly, seems to relate often to work reported in 1985/86. The ultrasound pictures are of good quality and well labelled so that they are easily interpreted. Some sections seem a bit sparse, the fetal cardiac measurements being especially scanty.

Of greatest importance are the recommendations that occur at the end of nearly every section although, since one of the expressed aims of the book was to provide guidance, I think that they could have been more comprehensive. While this book may have a place in the library of departments of medical ultrasound it may be of limited value to individual ultrasonologists.

M. J. Whittle

Immunobiology of Normal and Diabetic Pregnancy, Edited by D. Andreani, G. Bompiani, U. Di Mario, W. P. Faulk & A. Galluzzo. John Wiley and Sons, Chichester, New York, 1990, 329 pages, with figures and tables, £35

This book was a good idea when conceived but has failed to reach maturity. The justification was a desire to update the reader on the many advances in immunobiology of normal pregnancy, and immunopathology of abnormal pregnancy. It was felt that the specific immunopathology of insulin dependent diabetes was a well investigated model that could be used for comparison.

The resulting book bears the hallmarks of an edited symposium, but apparently there was no symposium. The contributions are of varying length and quality while some are review

articles, others contain detailed research findings. Most of the authors confine themselves to human pregnancy but there are extensive reports of a rat model of the heritability of diabetes, and another contribution is on insulin and IGF stimulation of receptors in chick embryos. Some contributions are of considerable interest, such as those of Ober & Weitkamp on the immunogenetics of normal and abnormal pregnancy, and Clark on models of normal and aborting pregnancy. Torry & McIntyre's contribution on the role of antibody in pregnancy includes an interesting review of the antiphospholipid antibodies in pregnancy failure. Three chapters later Triplett contributes on obstetrical complications associated with antiphospholipid antibodies and explains the problems of standardization and reproducibility of the lupus anticoagulant assay.

Labarrere & Page-Faulk review their work on immunology of the extra-embryonic tissues in normal and abnormal pregnancy in two chapters. They draw the conclusion that immunopathological findings in abnormal placentae are qualitatively similar to those in normal pregnancy, raising the possibility that immunological amplification may form a continuum between normality and abnormality.

While there is much comment to support the idea that immunological phenomena are significant in recurrent spontaneous abortion there seems to be a long way to go as judged by the following quotes from the book: 'In primary recurrent spontaneous abortion (no live children) there is a lack of a measurable allogeneic response to their mates lymphocytes, but secondary recurrent spontaneous aborters (at least one viable pregnancy in past) appear to mount immunological recognition of their mates which is far more intense and persistent than that usually observed in normal pregnancy'. And later, in another chapter, 'the possibility that aberrant antigen expression can lead to recurrent spontaneous abortion in humans remains an attractive but unproven concept'.

The section of the book on diabetes may be summed up by a quote from Galluzzo's chapter on cell mediated immunity in diabetic pregnancy, as he says, 'Although both diabetologists and immunologists consider this field of great interest, very few data are available'.

There is some interesting information in this book but I do not feel able to recommend it in its current format.

Robert Fraser

Psychological Processes of Childbearing, by Joan Raphael-Leff. Chapman & Hall, London, 1990, 566 pages, £19.95

This is the first book to provide an overview of all aspects of the psychology of pregnancy, birth and the postpartum period, and is likely to become a classic for doctors, midwives and other caregivers. Raphael-Leff is a psycho-analyst who worked with the MRC as a social-psychologist for fifteen years, and her main focus is on the relation between fantasies and behaviour and on the unresolved conflicts evident in transitional phases of life.

One of her aims is to write so that those who care for women are able to get in touch with their own feelings. She believes that this 'may help . . . to alleviate an intrusive spillover of their own personal needs, thereby helping to contain such feelings as rivalry, envy and exposure to suffering and intense emotions. Only self-knowledge can provide insight into one's own motivation for being a birth attendant, and self-knowledge can transform a crippling unconscious compulsion into liberating self-confidence.'

Her reiterated emphasis on the distinction between contrasting personality types which she calls 'Facilitators' and 'Regulators' may prove irritating to the reader by about page 295. Any *Weltanschauung* based on the premise that there are two types of people and all understanding of human behaviour can be organized according to this binary classification must be suspect.

Her material is well-organized, she begins with 'pregnancy expectations', 'pregnancy', and 'the expectant partner', including lesbian partners, and discusses social context of the transition to parenthood. Then she explores experiences of birth, goes on to 'coping with the outcome', and ends with 'complications', including under this heading a discussion of miscarriage, abortion and stillbirth, as well as violence, sexual abuse and depression. She summarizes key points at the end of each chapter, and relates her findings to possible action to improve the care given to childbearing women.

In short, a book which will be a useful teaching tool and essential reading for those engaged in intrapartum care.

Sheila Kitzinger

Books received some of which may be reviewed at a later date

Clinical Gynaecology edited by Thankam R. Varma. Edward Arnold, London, 1991, 1053 pages fully illustrated, £95.00

Anesthetic and Obstetric Management of High-Risk Pregnancy edited by Sanjay Datta. Mosby Year Book, St Louis, London, 1991, 719 pages with figures and tables, £53.00

A Practical Guide to Chorion Villus Sampling edited by David T. Y. Liu. Oxford University Press, Oxford, 1991, 115 pages illustrated, £15.00 paperback

Color Atlas of Colposcopy Third Edition by Hanskurt Bauer. Igaku-Shoin, New York, Tokyo, 1990, 226 pages illustrated with 314 plates 156 in colour, £65.00

Baillière's Clinical Obstetrics and Gynaecology Volume 5, Number 1 1991. Factors of Importance for Implantation edited by M. Seppälä. Baillière Tindall, London, pages 1-256 with figures and tables, £27.50 single issue, £55.00 annual subscription

Cytopathology of the Uterine Cervix by Alexander Meisels & Carol Morin. Published by the American Society of Clinical Pathologists and distributed outside the U.S. and Canada by Raven Press, New York, 1991, 351 pages fully illustrated with colour plates, \$170.00

Transvaginal Color Doppler: A Comprehensive Guide to Transvaginal Color Doppler Sonography in Obstetrics and Gynecology edited by Asim Kurjak. Parthenon Publishing Group, Carnforth, Lancs, 1991, 144 pages illustrated with colour plates, £65.00

Handbook of British Anaesthesia edited by Graham Smith. Professional and Scientific Publications, BMA House, Tavistock Square, London WC1H 9RJ, 114 pages, £14.95 UK, £16.50 Abroad

International Travel and Health. Vaccination Requirements and Health Advice World Health Organization, Geneva, 1991, 95 pages, Sw fr 14.00, US \$12.60

Nutrition During Pregnancy Part I Weight Gain. Part II Nutrient Supplements Institute of Medicine, National Academy Press, Washington, D.C., 1990, 475 pages with figures and tables, \$34.95

Exercises in Fetal Monitoring by Barry S. Schifrin. Mosby Year Book, St Louis, 1990, 183 pages illustrated, £23.50

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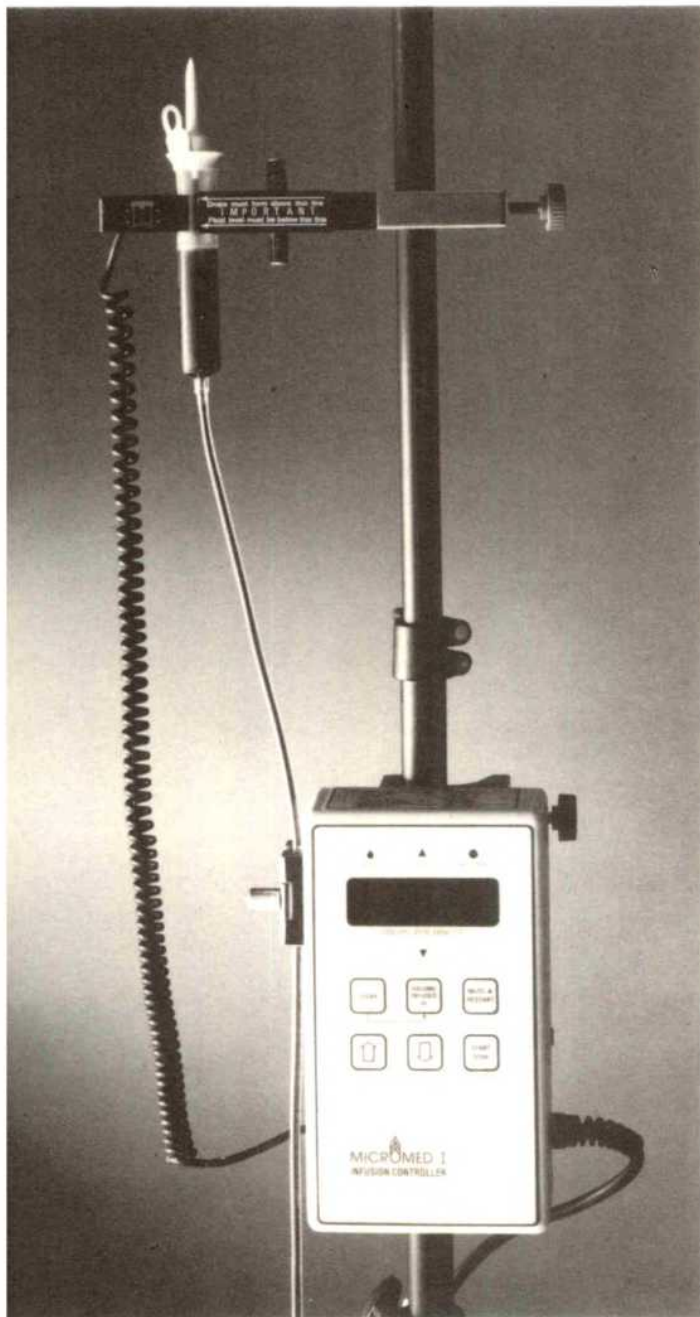
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British Journal of Obstetrics and Gynaecology

Vol 98 No 7 July 1991

CONTENTS

- 617 Commentaries
Quality of the perinatal autopsy
J. S. Wigglesworth
Management of tubal infertility in the 1990s
H. Reiss
- 624 West Midlands perinatal mortality survey, 1987. An audit of 300 perinatal autopsies
D. I. Rushton
- 628 An analysis of factors influencing the outcome of 232 consecutive tubal microsurgery cases
V. Singhal, T. C. Li & D. Cooke
- 637 Microsurgical salpingostomy is not an obsolete procedure
R. M. L. Winston & R. A. Margara
- 643 Is GIFT (gamete intrafallopian transfer) the best treatment for unexplained infertility?
A. P. Murdoch, M. Harris, M. Mahroo, M. Williams & W. Dunlop
- 648 Placental bed spiral arteries in the hypertensive disorders of pregnancy
R. Pijnenborg, J. Anthony, D. A. Davey, A. Rees, A. Tiltman, L. Vercruyssen & A. Van Assche
- 656 The variation of endometrial response to a standard hormone replacement therapy in women with premature ovarian failure. An ultrasonographic and histological study
T. C. Li, P. Dockery, S. S. Ramsewak, L. Klentzeris, E. A. Lenton & I. D. Cooke
- 662 The place of oophorectomy at vaginal hysterectomy
S. S. Sheth
- 667 Delivery in an obstetric birth chair: a randomized controlled trial
P. Crowley, D. Elbourne, H. Ashurst, J. Garcia, D. Murphy & N. Duignan
- 675 Partial placenta membranacea
B. S. Wilkins, G. Batcup & P. S. Vinall
- 680 Autoreactivity in women with endometriosis
P. V. Taylor, M. D. Maloney, J. M. Campbell, S. M. Skerrow, M. M. C. Nip, R. Parmar & G. Tate
- 685 Maternal plasma corticotrophin-releasing hormone—elevated in preterm labour but unaffected by indomethacin or nylidrin
T. Kurki, T. Lqätkäinen, K. Salminen-Läppäläinen & O. Ylikorkala
- 692 Prediction of lethal pulmonary hypoplasia and chorioamnionitis by assessment of fetal breathing
A. Ohlsson, K. Fong, M. Hannah, Z. Heyman, R. Gonen, T. Rose & R. Baboolal
- 698 Maternal angiotensin sensitivity and fetal Doppler umbilical artery flow waveforms
C. M. Cook & B. J. Trudinger
- 703 Vulvar vestibulitis syndrome: a clinico-pathological study
C. B. Furlonge, R. N. Thin, B. E. Evans & P. H. McKee
- 707 A comparative study of ethamsylate and mefenamic acid in dysfunctional uterine bleeding
G. Chamberlain, R. Freeman, F. Price, A. Kennedy, D. Green & L. Eve
- 712 Quantitative production of prostaglandin E_2 and its metabolites by human fetal membranes
H. Khan, M. H. F. Sullivan, R. Helmig, C. K. Roseblade, N. Uldbjerg & M. G. Elder
- 716 The role of postnatal x-ray pelvimetry after caesarean section in the management of subsequent delivery
S. Krishnamurthy, F. Fairlie, A. D. Cameron, J. J. Walker & J. R. Mackenzie
- 719 Pregnancy after orthotopic liver transplantation. Case report
N. C. W. Hill, N. H. Morris, R. W. Shaw, S. Mathur, K. Rolles & A. K. Burroughs
- 722 Congenital afibrinogenemia and successful pregnancy outcome. Case report
A. K. Trehan & I. L. C. Fergusson
- 725 A maternal death caused by AIDS. Case report
P. D. Kell, S. E. Barton, D. E. Smith, M. Nelson, R. P. Marwood & B. Gazzard
- 728 Overlap syndrome and its implications in pregnancy. Case report
K. S. Oláh & C. W. G. Redman
- 731 Short communications
Cervical preparation with gemeprost for dilatation and evacuation
J. A. D. Spencer, P. Nicolaidis, A. Lee, U. Nicolini & C. H. Rodeck
Early endometrial carcinoma: an incidental finding after endometrial resection. Case report
N. A. Dwyer & G. M. Stirrat
Use of intra myometrial 15-methyl prostaglandin $F_{2\alpha}$ to control atonic postpartum haemorrhage following vaginal delivery and failure of conventional therapy
A. Bigrigg, D. Chui, S. Chissell & M. D. Read
- 737 Correspondence
- 744 Book reviews

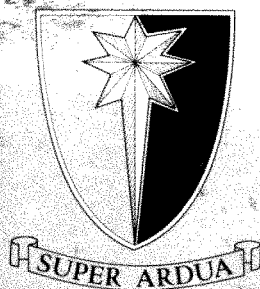
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COMMENTARY

Progestogens, lipid metabolism and hormone replacement therapy

The addition of a progestogen to oestrogen hormone replacement therapy (HRT) for postmenopausal women is now considered mandatory for protection of the endometrium against proliferation, hyperplasia and neoplasia. Recently, concerns about the metabolic effects of progestogens have led some practitioners, especially those in the USA, to advise against their use. Reductions in protection against coronary heart disease (CHD) of between one third and one half (Henderson *et al.* 1988, Roche & Vessey 1990) have been advanced as a consequence of combined therapy. However, the basis for these concerns is weak.

Almost all epidemiological studies have shown that postmenopausal use of unopposed oestrogen (usually conjugated oestrogens) reduces CHD morbidity and mortality by 50% or more (Ross *et al.* 1990). In the Lipid Research Clinics Program Follow-Up Study (Bush *et al.* 1987), the major study in which metabolic risk markers were assessed, the greatest single protective factor was the ability of oestrogen to induce changes in the plasma lipoprotein profile. Oestrogens shift the distribution of cholesterol within the various lipoprotein fractions, leading to a decrease in levels of low density lipoproteins (LDL) and an increase in those of high density lipoproteins (HDL), changes consistent with a protective effect on the arterial wall (Godsland *et al.* 1987). Indeed, the increase in HDL alone has been held to account for much of this beneficial effect. Clinical studies, often of short duration, have shown that many progestogens are able to oppose such changes, particularly in HDL, and this has raised fears over whether the beneficial effects of unopposed oestrogen will be negated by the addition of a progestogen.

To assess the impact of progestogens on cardiovascular disease, we must first examine the effects of combined therapy both on lipoprotein metabolism and on the various other mechanisms

whereby oestrogens are thought to exert their beneficial actions. What are these other mechanisms? Oestrogen effects on insulin and glucose metabolism, coagulation and fibrinolysis, the prostaglandin/thromboxane system and arterial blood flow have all been held to contribute to protection against CHD (Stevenson 1990). Comprehensive studies which would show whether progestogens affect these areas are sparse. Such data are urgently needed in the absence of controlled trials of unopposed oestrogen versus combined therapy; although these mechanisms are held to account for 50% of protection against CHD, they appear to have been overlooked in the present debate.

Current concepts of plasma lipoproteins assign risk to increased levels of triglycerides and LDL and decreased levels of HDL. In addition, minor fractions such as an LDL-related lipoprotein, Lp_a, and chemically modified forms of LDL, such as oxidized LDL, have been implicated in the pathogenesis of CHD. In the latter instances there is no published evidence either that oestrogens alone exert a beneficial effect, or that progestogen addition exerts a negative effect. We will deal with the more conventional risk factors each in turn.

Levels of high density lipoprotein predict future CHD in both men and women (Jacobs *et al.* 1990). Increasing HDL would be expected to protect against CHD, although drugs specifically designed for this purpose have yet to emerge. The concept that currently-prescribed relatively low doses of postmenopausal oestrogens will induce substantial increase in HDL may be challenged, given that these effects are dose-related. Oestrogen-induced increases in HDL that match the differences seen between users and nonusers in the Lipid Research Clinics study have not been reproduced in most of metabolic studies (Bush & Miller 1986). Furthermore, non-oral routes of administration do not induce the

increases in HDL seen with oral therapy. Where increases in HDL are seen in short-term metabolic studies, there is little evidence that they are maintained over decades. If oestrogens do raise HDL in all women, does the use of combined therapy negate this? By analogy with developments in oral contraception (Godsland *et al.* 1990), an appropriate choice of progestogen will allow the oestrogen effect on HDL to be maintained. There are further uncertainties. Does progestogen addition lower HDL levels irreversibly, and is the reduction of clinical significance since most postmenopausal women have satisfactory levels of HDL?

In contrast to its effects on HDL, the ability of oestrogen to reduce LDL levels is well accepted (Bush & Miller 1986). Addition of progestogen to oestrogen HRT does not negate the ability of oestrogens to lower LDL. On the contrary, the oestrogen-induced falls in LDL may be accentuated by the progestogen (Farish *et al.* 1986; Jensen *et al.* 1987; Crook *et al.* 1991).

Oral oestrogens increase triglycerides whereas progestogens may oppose this (Godsland *et al.* 1987). Although the precise role of triglycerides in the pathogenesis of CHD is controversial (Avins *et al.* 1989) it is likely that in this respect combined therapy will prove more beneficial than unopposed oestrogen.

Overall, we would conclude that use of combined therapy will not necessarily reduce any effects on HDL if a suitable progestogen is used; it would not negate any benefit bestowed by lowering LDL; and it may have a beneficial effect on triglycerides.

Progestogens are used in HRT in order to induce cyclic bleeding or in some cases amenorrhoea. Without proper bleeding control, HRT would be unacceptable to most postmenopausal women. Inappropriate rejection of the use of progestogens on unproven grounds of loss of protection against CHD would mean that many postmenopausal women would no longer receive the benefits of oestrogen therapy on climacteric symptoms or on osteoporosis.

Combined oestrogen/progestogen replacement therapy has been used extensively in the UK and the USA for more than a decade. Population studies of the effects of this therapy on cardiovascular disease are overdue

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Fetal heart block associated with maternal anti-Ro (SS-A) antibody—current management. A review

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The relation between maternal connective tissue disease and complete congenital heart block (CCHB) in the fetus has been known for some time (Hogg 1957). Several groups have described serum antibodies to soluble ribonucleoproteins, anti-Ro (SS-A) and anti-La (SS-B), in the affected infants and their mothers (Kephart *et al.* 1981; Franco *et al.* 1981; Miyagawa *et al.* 1981), and subsequent studies have demonstrated the almost universal association of CCHB with either or both of these autoantibodies (Scott *et al.* 1983; Watson *et al.* 1984; Weston *et al.* 1982; Taylor *et al.* 1988; Gross *et al.* 1989; McCredie *et al.* 1990). The heart contains one of the body's highest concentrations of Ro (SS-A) antigen (Wolin & Steitz 1984; Harley *et al.* 1985; Deng *et al.* 1987), and IgG deposits have been found in the cardiac tissues of affected infants (Litsey *et al.* 1985; Lee *et al.* 1987). Anti-Ro antibodies have also been implicated in the aetiology of myocarditis and conduction defects in adults (Logar *et al.* 1990). The evidence suggests that a passively acquired auto-antibody, probably anti-Ro (SS-A), binds to an antigen in the fetal heart and produces inflammation and fibrosis in the cardiac conduction system.

The majority of fetuses with CCHB are detected incidentally when the condition is established and irreversible. It has been shown that CCHB is rare in offspring of pregnant women with clinically apparent systemic lupus

erythematosus (SLE) associated with anti-Ro (SS-A) or anti-La (SS-B) antibodies (Lockshin *et al.* 1988). Most cases occur in women with sub-clinical connective tissue disease that may not become evident for some time (Reichlin *et al.* 1988; Petri *et al.* 1989). Thus, it is difficult to identify the group of women who would benefit from therapeutic intervention to lower the amount of the pathogenic maternal antibody available for transfer to the fetus before the development of CCHB. However, such treatment may be warranted in an identified high risk population.

Risk factors include:

1. A previous child affected with CCHB. The risk of having a child with CCHB in a woman with anti-Ro (SS-A) antibodies and no previous children with CCHB is 1 in 20 (Ramsey-Goldman *et al.* 1986). The risk of a subsequent pregnancy being affected, given the persistence of conditions leading to the index case, is about 1 in 3 pregnancies (Buyon *et al.* 1988; McCune *et al.* 1987), although this refers only to cases of *complete* heart block. ECG screening of 'non-affected' siblings may reveal clinically silent (1° and 2° AV block) conduction disturbances, the presence of which may increase the risk of heart block occurring in the current pregnancy. No such study has yet been reported.

2. High titres of anti-Ro antibody. There is still much debate about the maternal antibody titre at which a fetus is considered to be at risk of developing CCHB. One study has suggested a titre of > 1:16 to be of significance (Ramsey-Goldman *et al.* 1986).

3. The presence of anti-La (SS-B) antibody in addition to the anti-Ro (SS-A) antibody (Provost *et al.* 1987; McCredie *et al.* (1990).

4. Presence of HLA DR3 in the mother (Watson *et al.* 1984; Lee *et al.* 1983; Buyon *et al.* 1987; Buyon *et al.* 1988; Lockshin *et al.* 1983). Ro (SS-A) positive women giving birth to normal infants (i.e., absence of CCHB or neo-

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natal lupus) are generally HLA-DR2 (Watson *et al.* 1984).

The fetal circulation compensates for the reduction in heart rate by increasing cardiac stroke volume (Crombleholme *et al.* 1990; Koyanagi *et al.* 1990). The majority of these babies are therefore viable, although an associated myocarditis may result in cardiac decompensation. A pericardial effusion may appear as a result of cardiac failure or as part of an inflammatory response (Richards *et al.* 1990).

The treatment of patients with anti-Ro antibody would therefore fall into two categories: (i) prophylaxis for women who are considered to be carrying a fetus at high risk of developing heart block and (ii) treatment comprising the monitoring and delivery of a fetus with heart block *in-utero* in whom there is evidence of a progressive inflammatory condition.

The treatments that have been proposed are intended to decrease the quantity of pathogenic maternal antibody, and diminish the fetal myocarditis and the specific inflammation of the cardiac conduction system. Plasmapheresis has been recommended to limit cardiac damage upon recognition of an enlarging heart, pericardial effusion or conduction disturbances in the fetus (Buyon *et al.* 1987), but it is unsuccessful in reversing established fetal heart block (Herremann & Galezewski, 1985; Buyon *et al.* 1987). In high risk pregnancies it has been suggested that thrice weekly plasmapheresis in addition to steroids be started prior to 20 weeks gestation before antibody passage across the placenta increases in advance of the appearance of overt fetal disease (Buyon *et al.* 1989). Plasmapheresis (Buyon *et al.* 1988) and plasma exchange (Barclay *et al.* 1987) have been used safely in this context, but the use of plasmapheresis alone in high risk cases has not been reported. Such treatment regimens are based on a theoretical concept of the immunopathology of this condition. The quantity of IgG that is transferred transplacentally greatly increases towards the last trimester, such that only modest levels in the fetus are achieved before 22 weeks gestation (Stiehm 1975). It is not at all certain when CCHB first occurs; most cases are detected after 20 weeks gestation, but this may be a result of our current obstetric screening practice. A prospective study of patients with anti-Ro (SS-A) antibodies from the first trimester onwards may answer this question.

The use of steroid therapy to limit the inflam-

matory response in the fetal cardiac conducting system is well described (Buyon *et al.* 1987; Buyon *et al.* 1988; Barclay *et al.* 1987; Fox & Hawkins 1990). Dexamethasone is to be preferred to prednisolone as this leads to higher steroid concentrations in the fetal circulation (Blandford & Murphy 1977). However, the use of steroids is associated with problems such as maternal diabetes (Fox & Hawkins 1990), potential opportunistic infection and the prospect of poor healing in the fetus should surgery be required for pacing after birth. Thus, steroids should not be used unless there is good reason to believe there would be significant benefit. For this reason prophylactic therapy for all women with anti-Ro antibodies is not recommended. In addition, in cases of established CCHB, there is no evidence to suggest that steroids should be used unless there is evidence of a progression in the disease.

Immunosuppressive agents have not been used in the treatment of patients with anti-Ro antibody, but theoretically may be of some benefit. Azathioprine has been reported to be safe during pregnancy in renal transplant recipients (Davidson & Guillon 1984), patients with SLE (Meehan & Dorsey 1987) and in those with inflammatory bowel disease (Alstead *et al.* 1990). Treatment or prophylaxis using such agents may be a useful option, and warrant further study.

The identification of a fetal cardiac dysrhythmia should prompt an investigation for maternal anti-Ro and anti-La antibodies in addition to associated factors, such as lupus anticoagulant which may have an adverse effect on the pregnancy. Cardiac anatomy should be assessed initially to exclude an anomaly. A high resolution ultrasound scan with a two dimensional echocardiographic assessment is adequate to inspect major intrathoracic structures and may be combined with M-mode scanning to confirm the diagnosis of CCHB. In addition, any pleural or pericardial effusions will be detected. Doppler colour flow mapping may be used to identify blood flow patterns within the heart and the great vessels, thus adding to the accuracy of antenatal cardiac assessment (Sharland *et al.* 1990). Doppler velocity waveforms obtained from the inferior vena cava represent the right atrial activity while that of the aorta reflects the ventricular rate. Because of the close proximity of the two vessels, simultaneous recordings can be made to confirm the diagnosis of CCHB when

other forms of assessment have proven unsatisfactory (Chan *et al.* 1990).

Once fetal heart block due to anti-Ro (SS-A) antibody is established, careful monitoring of the fetal condition is essential. Cardiotocography is generally unhelpful in CCHB as the resulting pattern is unreactive with little variability (Beall & Paul, 1986; Oláh & Redman 1991), although it does indicate the baseline fetal heart rate. A mild bradycardia with reactivity has been reported (Fox *et al.* 1990), but this pattern was not due to heart block, and may have been an idiopathic benign sinus bradycardia. Doppler assessment of the umbilical artery is also of little value as, due to the prolonged diastolic component of the cardiac cycle, derived values depending on the time averaged velocity and ratios of the maximal frequency shifts in systole and diastole will be altered. Correcting these values to account for changes in the fetal heart rate is considered unnecessary when the rate is within the normal range (Hoskins *et al.* 1989; Kofinas *et al.* 1989; Newnham *et al.* 1990), but such corrections may have a clinical application in the fetus with CCHB (Oláh & Brown, unpublished observations). However, complete absence of flow during diastole will be apparent. This mode of examination would be particularly useful because of the association of anti-Ro antibodies with those connective tissue diseases, such as SLE, in which placental infarction and immunoglobulin deposition are frequently encountered (Hanly *et al.* 1988; Guzman *et al.* 1987). The increase in placental vascular resistance may be adequate to precipitate cardiac failure.

Biophysical assessment of the fetus with ultrasound examination of the fetal chest to detect pericardial and pleural effusions combined with M-mode echocardiography would appear to be the best way to monitor the fetus. M-mode echocardiography may also provide valuable information on left ventricular function such as stroke volume, cardiac output and ejection fraction (Veille *et al.* 1990). Additional analysis of fetal cardiac haemodynamics may be obtained by Doppler echocardiography (Takamiya *et al.* 1989). Valvular insufficiency will be detected by such techniques, and peak systolic velocities in the ascending aorta help to provide indirect information on cardiac output. Measurement of the cardiothoracic ratio by two dimensional echocardiography should be considered part of the antenatal assessment of structural or func-

tional fetal heart disease (Paladini *et al.* 1990). The degree of increase of this index from the normal range may assist in predicting the extent of lung compression and the severity of any existing cardiac failure. The aim of such intensive monitoring is to achieve fetal maturity without allowing cardiodynamic compromise. The combination of immaturity and the resulting respiratory distress syndrome with fetal heart block results in a high perinatal mortality.

Delivery is indicated when it is obvious that the fetal condition is deteriorating despite medical therapy, or when other obstetric indications supervene. As long as the fetus is otherwise healthy, and continues to be so with careful monitoring, spontaneous labour can be awaited. Because of the difficulty of diagnosing fetal distress when the fetal heart is not under autonomic control, and because some fetuses may suffer haemodynamic compromise compounded by labour, caesarean section has been advocated (Stewart *et al.* 1983; de Swiet 1984). However, more recently vaginal delivery has been shown to be safe (Beall & Paul 1986; Chatterjee *et al.* 1985; Baxi *et al.* 1987) and may be achieved with continuous heart rate monitoring and fetal blood sampling in labour. Intrapartum monitoring has also been achieved by recording the ventricular rate via a scalp electrode, and observing the atrial rate (which is still under autonomic control) through an external transducer (Chan *et al.* 1990). Other techniques reported include continuous intrapartum M-mode echocardiography (Todros *et al.* 1990), assessment of the pre-ejection period (onset of the Q wave of the ECG to the opening of the aortic valve) using the fetal ECG and Doppler ultrasound (Smith *et al.* 1990) and continuous transcutaneous P_{CO_2} measurement and laser spectroscopy (Decleer *et al.* 1990). The current development of pulse oximetry for use in labour has potential in this context.

The optimum management for the patient with anti-Ro (SS-A) antibodies has not been determined. Prophylactic management in the hope of avoiding or delaying the development of heart block is not without its side effects, and there is no reliable method of identifying the fetus at risk. The complexity of monitoring the fetus with heart block in order to achieve the right balance between the disease process and immaturity requires centralization of care. The collection of data and development of clinical management will require multicentre collabora-

tion with the combined expertise of obstetricians, paediatricians and rheumatologists with laboratory and ultrasound backup. In this way expertise in this rare condition will be concentrated, and experience will result in improvements in fetal outcome.

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Companionship to modify the clinical birth environment: effects on progress and perceptions of labour, and breastfeeding

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Abstract

Objective—To measure the effects of supportive companionship on labour and various aspects of adaptation to parenthood, and thus by inference the adverse effects of a clinically orientated labour environment on these processes.

Design—Randomized controlled trial.

Setting—A community hospital familiar to most of the participants, with a conventional, clinically-orientated labour ward.

Subjects—Nulliparous women in uncomplicated labour.

Intervention—Supportive companionship from volunteers from the community with no medical nor nursing experience, concentrating on comfort, reassurance and praise.

Main outcome measures—Duration of labour, use of analgesia, perceptions of labour and breastfeeding success.

Results—Companionship had no measurable effect on the progress of labour. Diastolic blood pressure and use of analgesia were modestly but significantly reduced. The support group were more likely to report that they felt that they had coped well during labour (60 vs 24%, $P < 0.00001$). Their mean labour pain scores (26.0 vs 44.2, $F < 0.00001$) and state anxiety scores (28.2 vs 37.8, $P < 0.00001$) were lower than those of the control group. Compared with the control group ($n = 75$), at 6 weeks women in the support group ($n = 74$) were more likely to be breastfeeding exclusively (51 vs 29%, $P < 0.01$); and to be feeding at flexible intervals (81 vs 47%, $P < 0.0001$).

Conclusions—Labour in a clinical environment may undermine women's feelings of competence, perceptions of labour, confidence in adapting to parenthood and initiation of successful breastfeeding. These effects may be reduced by the provision of additional companionship during labour aimed to promote self-esteem.

There is increasing recognition of the impact of social factors on health (Editorial 1988; Schwarzer & Leppin 1989). Modern obstetrics has

tended to isolate labouring women from the community contacts that were a feature of childbirth in preindustrialized societies (Kennell &

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Klaus 1988). In recent years, policies in many hospitals have been revised and companions, usually male partners, have been encouraged to be present during labour. There is little well-controlled evidence that the presence of male partners has a favourable effect on the progress of labour or its outcome (Keirse *et al.* 1989). The observable support given by first-time fathers has been unfavourably compared with that provided by female labour companions or 'douglas' (Bertsch *et al.* 1990).

The provision of medical care for childbearing women has been associated with improvements in the immediate outcome of pregnancy for mothers and their babies. At the same time, problems following childbirth such as failure to breastfeed successfully, failure to cope well as a mother and postnatal depression are widespread. It is important to question the extent to which modern-day obstetric practices contribute to either the positive or the negative features of contemporary childbirth (Oakley 1980).

Klaus *et al.* (1986) have shown that women from a rural background admitted to a large, western style hospital in Guatemala experienced considerably shorter labours and fewer complications when randomly assigned to receive continuous support from a female companion during labour. The extent of the improvements observed may be viewed as a measure of the extent to which those without the companionship were failing to achieve their biological potential and, therefore, as an indication of the adverse effects of the clinical environment on the labour process. Similar results have been reported from a public hospital in Houston serving a low-income population, with high use of technology and rates of intervention (Kennell *et al.* 1988). The potential for physiologically improved labour function may be less in environments in which the sense of isolation and unfamiliarity is less extreme than that described in the Guatemala study, or where medical interventions are less frequent than in the Houston study. On the other hand, there may be less obvious adverse effects of the conventional clinical environment on the process of labour and adaptation to parenthood.

Studies of general social support during pregnancy in industrialized communities have tended to show positive psychosocial benefits but a lack of demonstrable physiological improvements (Oakley 1989). In an affluent, low-risk North American population with high

rates of obstetric intervention, intrapartum professional support was associated with significantly reduced use of analgesia and rate of episiotomy, but not reduced labour length nor rate of caesarean section (Hodnett & Osborn 1989).

We have investigated the hypothesis that during labour women may be uniquely vulnerable to environmental influences; that modern obstetric care may have an adverse effect on the progress of labour and on the development of feelings of competence and confidence; that this may in turn impair adjustment to parenthood and establishment of breastfeeding; and that this process may to some extent be reversed by the provision of positive support and companionship during labour.

Subjects and methods

The study was conducted at Coronation Hospital, a community hospital serving a low-income urban population. Advertisements were placed in the hospital and local churches asking for help from women prepared to act as labour supporters. The work was to be voluntary, though a nominal allowance to help with expenses would be paid (about £3 sterling per day). Twenty women responded and were interviewed by two of the authors (W-L.W. and G.J.H.). They were asked about their reasons for volunteering and their attitudes to childbirth and the need for emotional support during labour. Role-play was used to assess their ability to express empathy. Three were selected to act as labour companions. They were asked simply to stay with those labouring women to whom they were allocated as continuously as possible, and using touch and speech to concentrate on three primary functions: comfort, reassurance and praise.

Nulliparous women in established labour without significant obstetric complications whose cervixes were less than 6 cm dilated and who had no supportive companion with them were asked to participate in the study. The details of the study were explained, in particular that participants would have only a one in two chance of being accompanied during the rest of the labour by a companion. Baseline clinical details of the participants were recorded and a brief questionnaire completed. Blood pressure and pulse were measured using a non-invasive monitor (Dinamap, Critikon, Johnson & Johnson Ltd). Blood samples were collected from the

intravenous line that was routinely employed to ensure adequate hydration in nulliparous women in the labour ward.

Participants were then allocated by means of randomly ordered cards in sealed opaque envelopes to a study and a control group. Those in the study group were introduced to one of the supporters who stayed with her at least for several hours, and in most cases until her baby was born. Participants were enrolled in the mornings only, as the supporters were not expected to stay at the hospital after dark. In all other respects, the care received by both groups was identical. Clinical care was provided by the resident medical and nursing staff. The time nursing staff could spend with women in both groups was limited by the relatively small nursing complement in our busy labour ward.

One hour after enrolment, venous blood was again collected and the blood pressure and pulse measurements repeated. When possible, cord and maternal blood are collected at delivery. Details of the labour and delivery were obtained from the hospital notes.

The next morning, within 24 h of delivery, a structured interview was conducted by a clinical psychologist (W-L.W.). For all but the last few questions, which related to the support received in labour, the interviewer was blind to the allocation of each woman.

Letters were written to the participants reminding them to attend the 6 week postnatal clinic and, if they failed to do so, further letters were sent and telephone calls made. At the postnatal visit, a further interview was conducted. It was not possible to ensure that the interviewer was always blind to the group allocation, as sometimes the participants volunteered information which identified them as belonging to one or other group.

Statistical comparisons of continuous data were by the Mann-Whitney *U* test. Proportions were compared by means of the 95% confidence intervals (CI) of the odds ratios and the χ^2 -test.

The protocol was approved by the committee for research on human subjects of the University of the Witwatersrand.

Results

Of the 190 women approached, 189 agreed to participate in the study and 92 were randomly allocated to the support and 97 to the control group.

The randomization process succeeded in producing groups which were very well matched for all the baseline data recorded, except for a slight imbalance in the racial composition. This discrepancy was considered too small to have materially altered the results (Table 1). Similar proportions were unmarried (support 79%, control 81%), Protestant (64%, 64%), Catholic (16%, 15%), Moslem or Hindu (14%, 13%), previously employed (45%, 44%), scholars (9%, 13%), had household monthly incomes below £200 Sterling (73%, 64%) and had completed more than 10 years of education (63%, 64%). Similar proportions strongly acknowledged that they felt excited (46%, 47%), worried (43%, 38%), sad (15%, 8%), afraid (46%, 43%), in pain (78%, 84%) and anxious (41%, 42%), and appeared to be moderately (46%, 53%) or severely (12%, 12%) distressed.

One woman in the control group left the hospital before completing the 24-h questionnaire, and could not be traced.

The biochemical results and psychosocial follow-up of the mothers and their babies will be considered elsewhere. This report is concerned with the comparisons between the two groups relating to labour and its perception, and breastfeeding.

Labour companionship had no measurable effect on the frequency of uterine contractions 1 h after entry to the study, the rate of cervical dilatation in the first 4 h, the use of oxytocics and amniotomy, or the duration of labour (Table 2). One hour after enrolment the blood pressures in the control group were somewhat lower than in the support group, the difference between diastolic pressures being statistically significant. The fetal heart rate was also slightly but not quite significantly, lower.

The overall number who required analgesia with pethidine and hydroxyzine (Aterax) was not different, but the first dose after enrolment was required earlier in the control group, and there was a trend towards more in the control group needing a subsequent dose.

The rate of operative deliveries was similar in the two groups. Meconium-staining of the amniotic fluid at the time of spontaneous or artificial rupture of the membranes tended to be more common in the support group. All other measures of neonatal well being tended to favour the support group, but none of the differences was statistically significant.

In contrast to the modest measurable effects

Table 1. Baseline information expressed as mean (SE) values or proportions (%)

Variable	<i>n</i>	Support	<i>n</i>	Control
Age (years)	91	20.5 (0.36)	97	20.3 (0.28)
Gestation (weeks)	92	39.4 (0.16)	97	39.6 (0.13)
Labour induced	92	6 (6.5%)	97	4 (4.1%)
Draining amniotic fluid	92	75 (82%)	97	75 (77%)
Occipito-anterior	84	63 (75%)	91	61 (67%)
Blood pressure (mmHg)				
Systolic	92	130.7 (1.66)	92	128.0 (1.55)
Diastolic	92	75.5 (1.24)	97	75.6 (1.08)
Pulse (/min)	91	83.9 (1.34)	97	85.9 (1.57)
Cervix dilated (cm)	92	4.0 (0.13)	96	3.9 (0.11)
Contractions (/10 min)	92	3.4 (0.09)	95	3.5 (0.10)
Fetal heart rate (/min)	92	136 (1.37)	96	135 (1.14)
Low variability	92	9 (9.8%)	96	10 (10%)
Decelerations	92	13 (14%)	96	13 (13%)
Previous analgesia	92	41 (45%)	97	41 (42%)
Oxytocin augmentation	92	8 (8.7%)	97	10 (10%)
Race Asian	92	12 (13%)	97	13 (13%)
Black	92	7 (7.6%)	97	1 (1.0%)
Coloured	92	73 (79%)	97	83 (86%)

on the physiological progress of labour, the psychological responses and perceptions of the groups were strikingly different (Table 3). The day after delivery the trait anxiety score (Spielberger 1983) and the self-esteem score (Coopersmith 1967), which measure stable personality characteristics and should not be influenced by recent events, were the same in the two groups. The state (current) anxiety score was significantly reduced in the support group. Fewer in the support group described their labour pain as 'severe', and the McGill pain rating index for labour pain (Melzack, 1975) was about half that of the control group. Fewer described their pain at the time of questioning as 'moderate' or 'severe'. Fewer described the labour as 'very difficult' or 'much worse than they had imagined it would be', or felt that they had been 'very tense', while more felt that they had coped well with the labour.

At 6 weeks after delivery, women in the support group were significantly more likely to be breastfeeding their babies exclusively (Table 4). They were about four times less likely to report having experienced feeding problems, three times less likely to have started foods other than breast or bottled milk, and almost twice as likely to be feeding at flexible intervals rather than by schedule.

Comparison of the main reasons given for stopping breastfeeding showed that what distin-

guished the groups was the greater number in the control group who had stopped because of a perception of having inadequate breast milk.

To investigate the possibility that participation in the study without being allocated to receive support may have had an adverse effect on the control group, 30 women who were not enrolled prospectively in the study because they had been admitted in labour over a weekend or in the evening, but whose records showed that they would have met the criteria for enrolment, were approached the day after delivery, and all agreed to complete the 24-h questionnaire. The results in Table 5 show that their responses were very similar to those of the randomized control group, and different to those of the support group.

Discussion

The contribution of modern obstetric care to improved perinatal outcome must be accounted for by the benefits of effective medical interventions in those women with complications of pregnancy. What has been unique in the field of childbirth has been the application of clinically orientated care on a wide scale to healthy individuals. Labour in particular has been defined as a high-risk situation *de facto*, justifying the imposition of the restrictions of clinical care on a routine basis. It is important to question whether

Table 2. Details of labour outcome expressed as mean (SE) values or proportions (%)

Variable	<i>n</i>	Support	<i>n</i>	Control	<i>P</i>	Odds ratio (95% CI)
1 h after entry to study						
Blood pressure (mmHg)						
Systolic	87	125.3 (1.83)	95	132.1 (1.64)	0.19	
Diastolic	87	73.6 (1.15)	95	76.6 (1.16)	0.03	
Pulse	85	82.2 (1.57)	95	80.9 (1.55)	0.88	
Contractions/10 m	87	3.51 (0.10)	93	3.78 (0.12)	0.63	
Irregular	87	6 (6.9%)	93	4 (4.3%)	0.66	1.64 (0.46–5.8)
Fetal heart rate	87	134.5 (1.31)	94	136.8 (1.23)	0.052	
Low variability	87	8 (9.2%)	94	12 (12.8%)	0.28	0.70 (0.28–1.8)
Decelerations	87	17 (19.5%)	94	19 (20.2)	0.94	0.96 (0.46–2.0)
Amniotomy (total)	92	56 (71.7%)	96	69 (71.9%)	0.89	0.99 (0.53–1.9)
Hours after entry	16	2.2 (0.35)	22	2.5 (0.45)	0.92	
Cervix change (cm/h)	90	1.03 (0.09)	93	1.02 (0.10)	0.64	
Analgesia	92	52 (57%)	97	56 (58%)	0.98	0.98 (0.55–1.7)
Next analgesia (h)	52	2.33 (0.26)	56	1.67 (0.27)	0.03	
Analgesia >once	92	6 (6.5%)	97	13 (13.4%)	0.18	0.47 (0.18–1.2)
Oxytocin used	92	16 (17%)	97	17 (18%)	0.88	0.99 (0.47–2.1)
Hours after entry	16	4.43 (0.61)	17	3.92 (0.43)	0.65	
Labour duration (h)	92	9.6 (0.41)	97	10.2 (0.50)	0.63	
Entry-delivery (h)	92	5.18 (0.33)	97	5.24 (0.31)	0.94	
Assisted delivery	92	7 (7.6%)	97	7 (7.2%)	0.86	1.06 (0.36–3.1)
Caesarean section	92	11 (12.0%)	97	14 (14.4%)	0.77	0.81 (0.35–1.9)
Meconium-staining	92	18 (19.6%)	97	10 (10.3%)	0.11	2.07 (0.93–4.6)
Birthweight (g)	92	3093 (45.5)	97	3116 (42.5)	0.66	
1-min Apgar <7	87	12 (13.8%)	91	22 (24.2%)	0.08	0.50 (0.24–1.0)
5-min Apgar <7	89	4 (4.5%)	96	6 (6.2%)	0.42	0.71 (0.20–2.5)
Oxygen required	92	24 (26.1%)	97	27 (27.8%)	0.92	0.92 (0.48–1.7)
Baby intubated	92	0 (0%)	97	1 (1.0%)	0.51	0.14 (0.003–7)
Cord pH	74	7.23 (0.01)	75	7.23 (0.01)	0.80	
Cord base excess	75	9.21 (0.42)	74	9.09 (0.44)	0.61	

such profound manipulations of the childbirth environment might have unsuspected adverse

effects on the process of birth and adaptation to parenthood.

Table 3. Questionnaire responses within 24 h of birth expressed as mean (SE) values or proportions (%)

Variable	<i>n</i>	Support	<i>n</i>	Control	<i>P</i>	Odds ratio (95% CI)
Trait anxiety score	92	40.2 (0.94)	96	39.8 (0.90)	0.86	
State anxiety score	92	28.2 (0.85)	96	37.8 (1.10)	0.00001	
Self-esteem score	92	65.3 (1.80)	96	65.9 (2.01)	0.63	
Labour pain severe	92	53 (57.6%)	96	76 (79.2%)	0.002	0.37 (0.2–0.67)
Pain rating index	92	26.0 (1.42)	96	44.2 (1.52)	0.00001	
Pain at time of questioning						
Moderate	92	13 (20.7%)	96	33 (34.4%)	0.05	0.51 (0.3–0.96)
Severe	92	3 (3.3%)	96	23 (24.0%)	0.0001	0.18 (0.08–0.4)
Mothers' perceptions of labour						
Very difficult	92	32 (34.8%)	96	57 (59.4%)	0.002	0.37 (0.2–0.66)
Coped well	92	54 (58.7%)	96	23 (24.0%)	0.00001	4.17 (2.3–7.5)
Felt very tense	92	28 (30.4%)	96	62 (64.6%)	0.00001	0.26 (0.14–0.5)
Much worse than imagined	92	34 (37.0%)	96	62 (64.6%)	0.0003	0.33 (0.2–0.59)

Table 4. Questionnaire responses at 6 weeks postpartum

Variable	Support (n = 74)	Control (n = 75)	P<	Odds ratio (95% CI)
Found becoming a mother easy	33 (44.6%)	8 (10.7%)	0.001	5.42 (2.6–11.1)
Managing well with baby	67 (90.5%)	49 (65.3%)	0.001	4.27 (2.0–9.2)
Breastfeeding only	38 (51.4%)	22 (29.3%)	0.01	2.48 (1.3–4.8)
Not breastfeeding at all	16 (21.6%)	24 (32.0%)	0.21	0.59 (0.3–1.2)
On food other than milk	13 (17.6%)	40 (53.3%)	0.0001	0.21 (0.1–0.4)
Has had feeding problems	12 (16.2%)	47 (62.7%)	0.0001	0.15 (0.08–0.3)
Baby has poor appetite	0 (–)	19 (25.3%)	0.001	0.10 (0.04–0.3)
Flexible feeding intervals	60 (81.1%)	35 (46.7%)	0.0001	4.39 (2.3–8.5)
Main reason for starting bottle-feeding				
Return to work	3 (4.1%)	7 (9.3%)	0.34	0.43 (0.1–1.6)
Believes bottle better	8 (10.8%)	5 (6.7%)	0.54	1.68 (0.5–5.2)
Baby not satisfied or ill	4 (5.4%)	4 (5.3%)	0.73	1.01 (0.24–4.2)
Breast milk insufficient	10 (13.5%)	24 (32.0%)	0.01	0.35 (0.2–0.76)
Breastfeeding problems	10 (13.5%)	11 (14.7%)	0.97	0.91 (0.4–2.3)
Other	1 (1.4%)	2 (2.7%)	0.99	0.51 (0.05–5.0)

Results are expressed as proportions (%).

The dramatic effects on the physiological progress of labour found in the study of Klaus *et al.* (1986) did not occur in this study. This might be because the companionship provided was less effective, medical intervention was less frequent, or because the adverse environmental effects were less intense, creating less scope for improvement. The latter explanation is most likely, as the participants differed from those in the Guatemala study in that they were Western, educated urban working-class women in a familiar community hospital. On the other hand, the

reduction in labour duration and complications in a high-technology environment demonstrated in the study of Kennell *et al.* (1988) may in part have been related to the lower rate of medical interventions, particularly epidural analgesia, in their support group. Epidural analgesia was not available to our patients.

The direction of blood pressure changes in our study was consistent with reduced anxiety in the supported group, but these changes were small.

Companionship, however, had a striking effect on the way that the participants reported

Table 5. Comparison of randomized groups with retrospectively selected control group. Data expressed as mean (SE) values or proportions (%)

	Randomized groups				Retrospective control group	
	<i>n</i>	Support	<i>n</i>	Control		
1. Baseline data						
Age (years)	91	20.5 (0.36)	97	20.3 (0.28)	30	20.4 (0.47)
Gestation (weeks)	92	39.4 (0.16)	97	39.6 (0.13)	30	39.5 (0.18)
Unmarried	92	73 (79%)	96	78 (81%)	30	25 (83%)
Race: Asian	92	12 (13%)	97	13 (13%)	30	3 (10%)
Black	92	7 (7.6%)	97	1 (1.0%)	30	0 (–)
Coloured	92	73 (79%)	97	83 (86%)	30	27 (90%)
Education >10 years	92	58 (63%)	95	61 (64%)	30	21 (70%)
2. Outcome						
Labour duration (h)	92	9.6 (0.41)	97	10.2 (0.50)	30	12.2 (0.97)
Birthweight (g)	92	3093 (45.5)	97	3116 (42.5)	30	3250 (67.6)
Trait anxiety score	92	40.2 (0.94)	96	39.8 (0.90)	29	38.2 (2.1)
State anxiety score	92	28.2 (0.85)	96	37.8 (1.10)	30	36.7 (1.92)
Labour pain severe	92	53 (57.6%)	96	76 (79.2%)	29	23 (79.3%)

experiencing labour. The various measures of labour pain were significantly reduced in the support group, and analgesia was needed significantly later after entry to the study. Supported women reported far more frequently feeling that they themselves had coped well during labour. If feelings of competence initiated during labour, a time of intense emotional impressionability, are of importance to a woman's ongoing sense of competence as a mother and ability to breastfeed successfully, then this finding is of considerable importance.

In recent years, the direct benefits of breastfeeding for the physical health of babies have been increasingly recognized (Inch 1989). The possible contribution of successful breastfeeding to factors such as satisfaction and happiness in motherhood, the development of positive mother-infant relationships and the emotional development of babies are more difficult to measure; but may also be of importance. In communities without access to safe alternative feeding methods, breastfeeding success is literally a matter of life or death. The main cause of the high infant mortality rate in many such communities is gastroenteritis resulting directly from bottle-feeding (Irwig & Ingle 1984). If the provision of modern obstetric care for such communities has contributed to a significant increase in bottle-feeding, then the contribution to infant mortality may in fact outweigh any beneficial effects on perinatal mortality rates.

Breastfeeding success appears to be vulnerable to a number of direct and indirect factors. Review of the available evidence from randomized trials (Inch & Garforth 1989) has shown that breastfeeding success is adversely affected by restricted breastfeeding, giving free formula samples to breastfeeding mothers, combined oestrogen/progesterone contraception, and restricted mother-infant contact after birth (Thomson & Westreich 1989). It is promoted by general social support during pregnancy (Elbourne *et al.* 1989), antenatal breastfeeding education (Inch 1989) and postnatal support for breastfeeding mothers (Inch & Garforth 1989). Randomized trials of procedures not directly linked to breastfeeding but which depart from the conventional restrictions of the clinical environment have also been shown to have positive effects on breastfeeding success. These include ambulation during labour (Broadhurst *et al.* 1979) and early discharge from hospital (Hellman *et al.* 1962). These results indicate that

conventional hospital care may interfere with the development of the confidence needed to breastfeed successfully.

In our study, women in the support group experienced significantly greater breastfeeding success and fewer feeding problems, and were more likely to use a flexible approach to feeding times.

The possibility that factors other than the labour companionship could have accounted for these differences needs to be explored. The labour companions were not aware that breastfeeding was one of the end-points of the study, and it was confirmed in retrospect that they on no occasion discussed breastfeeding nor helped with the first feed after birth. They did not visit the participants in the postnatal wards. Occasionally participants would seek them out in the hospital and on one occasion at home, but only to show them how the baby was progressing, and breastfeeding advice was not given at this time either.

Differences in the progress of and interventions in labour might also have affected breastfeeding success. In fact, these were very small, except for slightly less use of analgesia in the support group.

The possibility must be considered that those who had received the labour support replied more positively to the subjective questions out of a desire to please the researchers. A good test of validity of the interview is given by the trait anxiety questionnaire, which is designed to measure long-term anxiety and should not be much affected by recent events. The consistency of these scores indicates that subjective bias between the groups is most unlikely.

To explain the pronounced and persistent effects on feelings, perceptions and behaviour of a relatively short-lived intervention, we need to accept the premise that labour is a time of unique sensitivity to environmental factors, and that events and interactions during labour may have far-reaching and powerful psychological consequences. Given the fact that very few human experiences approach in intensity the levels of stress, anxiety, pain, exertion and emotional tumult which occur during labour, this is not surprising.

We have attempted to analyse the characteristics of the labour support provided in this study. It was not informative except to the extent of simple advice derived from personal experience, as the companions had no medical, nursing

nor traditional midwifery experience, but all had children of their own. The factors we think were of importance are as follows: Firstly, the companions were not part of the hospital medical or nursing hierarchy, and therefore may have been seen as an ally without a vested interest in the hospital establishment. Secondly, they were drawn from the same community and would be able to communicate easily with and share common values with the participants. Thirdly, they were not known personally to the participants and this might have avoided feelings of having to meet expectations or keep up appearances which may occur when women are supported during labour by a friend, family member or known midwife or antenatal educator. Fourthly, the specific elements on which the companions were repeatedly reminded to concentrate were comfort, reassurance and praise. The last was emphasised because of our hypothesis that an important way in which the clinical environment might impair the process of birth and adaptation to parenthood might be by undermining women's sense of achievement and development of confidence as mothers. Fifthly, the emotional support given seemed to be genuine. The companions worked as volunteers (though the small expense allowance might have been a motive) and were selected on the basis of appearing to have a genuine desire to help women in labour. They showed a remarkable ability to maintain a commitment to their vocation, with the exception of one supporter who after some weeks became distracted by personal problems and was withdrawn from her supporting role. She was asked to help with clerical work instead. An illustration of the extent to which the support and praise given was genuine is provided by the response of one of the supporters to the one occasion on which a participant visited her at home and brought her a gift. She said that she felt guilty as she had really done nothing, it was the woman herself and the nursing staff who had done everything. And finally, quite apart from anything the companions did or said, the fact that someone with no other function whatsoever was allocated on a full-time basis to be with the women in labour may have conveyed a message of concern for and value of them as individuals.

How applicable are these results to other hospital situations? The participants were nulliparous and on the whole young, urban working-class women who were politically and socially disadvantaged. Many were single, and

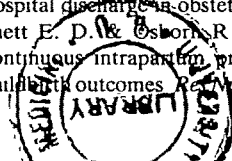
most were from a community with a conventional Christian ethic. It would be expected that the results would be directly applicable at least to urban working-class women giving birth in a hospital setting in most parts of the world. How best to adapt the principles established in this study to more affluent communities, and those with very different cultural mores, will need further assessment. Further research will also be necessary to determine whether similar effects result from support by other categories of companions, particularly if differing from those in this study by being non-voluntary workers, part of the hospital hierarchy or an associate of the women in labour. The role of male partners, in particular, involves complex and variable relationship factors that are difficult to assess.

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Prospective comparison of videopelviscopy with laparotomy for ectopic pregnancy

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Abstract

Objective—To compare operative laparoscopy with laparotomy for the management of ectopic pregnancy in haemodynamically stable women.

Design—Non-randomized prospective cohort study, treatment allocation depending on the surgical preference and experience of the on-call medical team.

Setting—Provincial undergraduate teaching hospital.

Subjects—87 consecutive and unselected haemodynamically stable women treated for ectopic pregnancy between 1 March 1988 and 31 August 1989.

Interventions—Salpingotomy, salpingectomy, salpingo-oophorectomy or simple extraction of the ectopic pregnancy depending on its site, size and nature performed under laparoscopic control or laparotomy

Main outcome measures—Operative outcome, duration of surgery, intra- and post-operative complications, post-operative hospital stay, return to normal domestic activities, return to work, changes in plasma β -hCG concentrations, health and social service costs.

Results—60 women were treated by videopelviscopy on 65 occasions and the other 27 were treated by laparotomy. The two groups were similar for age, parity and gestation at presentation. Of the 65 operative laparoscopies 61 (94%) were successful and all 27 laparotomies were completed uneventfully. Whereas the operating time was similar in the two groups, 55.3 and 51.1 min for videopelviscopy and laparotomy respectively, operative laparoscopy was associated with significantly shorter post-operative hospital stay (1.7 vs 5.2 days), faster return to domestic activities (1.5 vs 3.3 weeks) and work (2.5 vs 5.7 weeks) ($P < 0.001$ for all). In economic terms, successful videopelviscopy was associated with a reduction in hospital accommodation costs by 69% (£248 vs £808), drug costs by 52% (£8.38 vs £17.57) and statutory sickness payment by 51% (£130.25 vs £266.51), that is an overall saving to the health and social services of £701.47 or 50% per ectopic pregnancy ($P < 0.001$).

Conclusions—Operative laparoscopy can be used to successfully treat most cases of extrauterine pregnancy with advantages over laparotomy in terms of reduced hospitalization, faster recovery and lower health service costs.

Since Lawson Tait performed the first successful operation for ectopic pregnancy more than 100

years ago, laparotomy, with control of haemorrhage and removal of the trophoblast, has

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become the basis for treatment of this potentially fatal condition. Apart from minor modifications in technique and the appreciation of the role of conservative surgery, this approach changed little over the ensuing years. However, Shapiro & Adler (1973) opened a new chapter in therapy when they reported the excision of an ectopic pregnancy using the laparoscope. Laparoscopy had until then been used purely as a diagnostic aid, but with improvements in equipment and the development of special instruments, operative procedures such as salpingectomy and salpingotomy became possible (Semm 1978; Bruhat *et al.* 1980). The safety and efficacy of a laparoscopic approach to management have subsequently been confirmed by several series, treatment initially being restricted to small intact tubal pregnancies (Pouly *et al.* 1986; DeCherney & Diamond 1987). More recently, ruptured ectopic pregnancies have also been shown to be suitable for laparoscopic surgery provided there was no hypovolaemic shock (Reich *et al.* 1987; Magos *et al.* 1989).

Operative laparoscopy has a number of theoretical advantages over open abdominal surgery in terms of less discomfort, superior cosmetic appearance, a shorter hospital stay, faster recovery, reduced costs and, possibly, less morbidity. A recent retrospective case-control study of ectopic pregnancies from the USA has shown that the less invasive approach is associated with significantly reduced post-operative analgesia requirements, hospital stay and convalescence (Brumsted *et al.* 1988). To assess the two modes of management prospectively, we compared videopelviscopy (operative gynaecological laparoscopy in association with video monitoring) with the conventional sequence of diagnostic laparoscopy followed by laparotomy in women with ectopic pregnancy who were haemodynamically stable. We were particularly interested to find out whether the described benefits of endoscopic surgery apply irrespective of the degree of tubal damage. A further focus of the study was a detailed cost comparison of the two managements to assess the financial implications of videopelviscopic surgery for the health and social services.

Patients and methods

The study group consisted of a consecutive series of 87 women not clinically shocked, who were

treated on 92 occasions for extrauterine pregnancy at the Churchill Hospital, Oxford during the period of 1 March 1988 to 31 August 1989. Most of them presented with acute lower abdominal pain or pelvic tenderness, and were found to have a positive urinary pregnancy test (β -hCG concentration >50 IU/l) without evidence of intrauterine pregnancy on ultrasound examination. During the study period 14 women were excluded from the analysis because they were clinically shocked on admission and required immediate laparotomy.

Management

The mode of management was dictated by the surgical preference of the on-call team and was decided *before* laparoscopy. As a reflection of the interest in Oxford for less invasive surgery, intention to treat by videopelviscopy applied to 60 women and by laparotomy to 27.

Videopelviscopy

A total of 65 emergency videopelviscopies were performed by two of the authors (A.L.M. and R.B.) on the 60 women; two women underwent a second procedure for retained trophoblast tissue after salpingotomy, and three women were admitted with a further ectopic pregnancy on the contralateral side. The equipment and techniques for videopelviscopic management of ectopic pregnancy have been described in detail (Magos *et al.* 1989). All patients were counselled before surgery and consented for possible laparotomy.

Laparotomy

Patients in this group were operated on by registrars and senior registrars on call according to standard surgical techniques. Following laparoscopic confirmation of the diagnosis, a Pfannenstiel incision was made to remove the ectopic pregnancy. Drains were not used routinely.

Post-operative management

Both groups continued to be managed by their respective surgeons while in hospital. Early mobilization was encouraged, with discharge from hospital as soon as medically safe. Venous blood was taken within 12 h of surgery for plasma β -hCG, the assay being repeated after 1

and 6 weeks. All patients were seen in the outpatient department 6 weeks after surgery to assess their recovery, including the time taken to return to normal domestic activity and work. Tubal patency was also checked by hysterosalpingography 3 months after surgery in a subgroup of patients who had undergone linear salpingotomy.

Cost comparison

The courses of 20 randomly chosen patients from each treatment group with no pre- or post-operative complications, identified by random numbers, were analysed in detail with respect to the costs for accommodation, investigations, drugs, the use of operating theatres, and statutory sickness payment for those employed. Accommodation costs were estimated by multiplying the duration of post-operative hospital stay with the current daily charge for a gynaecological bed at the Churchill Hospital (£160), a figure which included expenses for nursing care and sanitary materials such as plasters and disinfectant solutions. Investigation costs included ultrasound examinations (£30), pregnancy tests (£1.10 for the sensitive RAMP test manufactured by Monoclonal Antibodies Inc, and £0.27 for the less sensitive Pregnosticon test manufactured by Organon Teknika BV), and pathology specimens (£6 for a full blood count, £6 for blood grouping, and £12 for histological examination of the operative specimen). Operating theatre charges were identical for both treatments (£270 per case) as videopelviscopic surgery and conventional laparotomy are both classified as 'major procedures'. Drug costs for patients were assessed individually based on a confidential price list issued by the principal pharmacist at the Churchill Hospital. No patient required post-operative blood transfusions. Statutory sickness payment for employed patients was calculated by multiplying the weekly DHSS standard rate of £52.10 with the number of weeks the patients stayed off work minus 3 days; 13 patients in each treatment group were entitled to this payment.

Statistics

Results for the two groups were compared using

two-tailed Student's *t*-test. A result was considered significant if $P < 0.05$.

Results

The two groups were similar in terms of age, parity, history of previous laparotomy, as well as gestation, size, site and state of the ectopic pregnancy, and volume of haemoperitoneum at the time of surgery (Table 1). The operative details of procedures carried out by videopelviscopy or laparotomy are summarized in Table 2. Whereas most patients managed by laparotomy underwent radical surgery (22/27), linear salpingotomy (29/65) and salpingectomy (28/65) were performed in almost equal frequency in the women treated laparoscopically, reflecting a preference for conservative surgery by the authors whenever appropriate. In fact, the 29 laparoscopic salpingectomies included eight procedures where salpingotomy was attempted, but continued bleeding from the site of the ectopic necessitated removal of the affected fallopian tube. Apart from primary treatment of the ectopic pregnancies, procedures such as ovarian cystectomy and adhesiolysis were also carried out during videopelviscopy ($n = 14$) and laparotomy ($n = 4$). The estimated operative blood loss was similar in the two treatment groups, as was the total operative time from intubation to extubation of the patient.

Overall, 61/65 (94%) of the videopelviscopies were completed successfully. Two women required immediate laparotomy, and a further two underwent a subsequent videopelviscopic salpingectomy after retained trophoblast following conservative surgery. The laparotomies included a 26-year-old woman with a chronic left sided ovarian ectopic pregnancy and a 600 ml organized haemoperitoneum, which could not be aspirated sufficiently for safe laparoscopic surgery, the same patient was readmitted 7 months later with a leaking right ampullary tubal pregnancy and successfully underwent videopelviscopic right salpingectomy. The second patient requiring laparotomy was a 21-year-old woman with a leaking right cornual pregnancy in whom a videopelviscopic attempt to resect the ectopic pregnancy failed because of arterial bleeding from the tube.

Apart from the two women with retained trophoblast, there were no serious complications in either group (Table 3). In contrast, post-operative hospital stay and recovery after videopel-

Table 1. Patient characteristics at the time of surgery

	Videopelviscopy (<i>n</i> = 60)		Laparotomy (<i>n</i> = 27)	
Number of patient procedures	65*		27	
Mean (SD) age (years)	28.2	(5.1)	28.9	(5.7)
Parous	34	(57%)	10	(37%)
Employed	42	(70%)	18	(67%)
Previous laparotomy	21	(35%)	10	(37%)
Mean (SD) gestation (weeks)	7.0	(1.9)	6.6	(1.2)
Mean (SD) size of ectopic (cm)	3.6	(1.4)	4.2	(2.1)
Site:				
Ampulla	55	(85%)	21	(78%)
Isthmus	5	(8%)	4	(15%)
Cornua	2	(3%)	2	(7%)
Ovary	3	(5%)	0	(-)
State:				
Intact	9	(14%)	3	(11%)
Leaking	40	(61%)	17	(63%)
Ruptured	12	(18%)	5	(18%)
Chronic	4	(6%)	2	(7%)
Mean (range) haemoperitoneum (ml)	112.5	(0-800)	181.2	(0-1000)

*Five patients had two separate procedures

viscopy was significantly shorter: most patients left hospital within 24 h of surgery, and were able to resume normal domestic activities on average 2 weeks earlier and return to work 4 weeks sooner than those who underwent laparotomy ($P < 0.001$ for all). Pelvic examination 6 weeks after surgery was unremarkable in most cases, adnexal or uterine tenderness being noted in four (7%) patients after videopelviscopy and two (7%) after laparotomy. Two other patients from the laparotomy group had some inoffensive discharge from their Pfannenstiel incision.

Analysis of plasma β -hCG concentrations showed no significant difference between the

treatment groups (Figure 1). One patient after videopelviscopic right salpingectomy for a 5 cm ruptured ampullary ectopic pregnancy had a β -hCG level of 653 IU/l at 6 weeks after surgery but repeat pregnancy tests 10 and 12 weeks later were negative, and the woman had a normal period 13 weeks after the operation. In the laparotomy group one patient who underwent expression of a 2.2 cm leaking isthmic ectopic pregnancy showed a β -hCG level of 11 IU/l at the 6 weeks follow-up appointment. She had a normal period 4 weeks after surgery and a normal hysterosalpingogram with free spill of contrast medium from both tubes 3 months

Table 2. Operative details

	Videopelviscopy		Laparotomy	
Number of procedures	65		27	
Grade of surgeon				
Senior Registrar	56		9	
Registrar	-		18	
Senior House Officer	19		-	
Salpingotomy	29	(45%)	2	(7%)
Salpingectomy	28	(43%)	20	(74%)
Extraction/expression	4	(6%)	3	(11%)
Salpingo-oophorectomy	1	(3%)	2	(7%)
Excision of ovarian pregnancy	1	(2%)	0	(-)
Laparotomy	2	(3%)	-	
Mean (SD) procedure time (min)	55.3	(17.8)	51.1	(15.8)
Mean (SD) operative blood loss (ml)	206.1	(235.9)	269.0	(258.9)

Table 3. Post-operative complications and recovery

	Videopelviscopy		Laparotomy	
Retained trophoblast	2		0	
Pelvic haematoma/infection	2		1	
Urinary tract infection	2		0	
Transient ileus	2		0	
Wound infection	0		5	
Mean (SD) post-operative hospital stay (days)	1.7	(1.2)	5.2	(1.4)
Mean (SD) return to normal activities (weeks)	1.5	(0.9)	3.3	(1.2)*
Mean (SD) return to work (weeks)	2.5	(1.5)	5.7	(1.6)*

* $P < 0.001$.

later. Eighteen (72%) of the women who underwent conservative surgery by videopelviscopy and two (29%) by laparotomy agreed to have a hysterosalpingogram 3 months after surgery; there was normal spill of contrast medium from the operated tube in 15 (75%).

The cost comparison of the 20 randomly chosen patients from each treatment group without per- or postoperative complications showed no significant difference for investigations in hospital or the use of theatre facilities (Table 4). Videopelviscopic surgery, however, reduced accommodation costs by 69%, drug costs by 52% and statutory sickness payments by 51%, which added up to an average overall saving to

the health and social services of £701.47 or 50% per patient ($P < 0.001$ for all).

Discussion

This prospective comparison of videopelviscopic management of ectopic pregnancy with laparotomy confirms many of the observations made by Brumsted *et al.* (1988) from the USA in their retrospective study using historical controls of laparoscopy versus laparotomy (Table 5). Both studies found significant reductions in hospital stay and faster convalescence after the less invasive approach; although the American authors also noted a reduction in the mean operating time with laparoscopy (77.5 vs 103.6 min), the reported operative time for laparotomy is well in excess of the typical times taken in our study.

Our continuing experience with videopelviscopy also confirms our initial observations and those of others (Reich *et al.* 1987; Magos *et al.* 1988, Silva 1988) that laparoscopic procedures need not be restricted to unruptured ectopic pregnancies less than 3 cm in diameter, as advocated by some (Sauer *et al.* 1988). In our study, 52 (80%) of the videopelviscopic procedures were carried out on tubal pregnancies which were leaking or ruptured, while the mean size of the pregnancies at surgery was 3.6 cm (range 1–10 cm). In presence of normal vital signs, laparoscopic surgery should be attempted in all cases, with the probable exceptions of large chronic extra-uterine and cornual pregnancies. It is likely, however, that future improvements in laparoscopic instruments for pelvic lavage and haemostasis will make even these rare cases possible.

Despite similar presentations, three quarters of the laparotomy group underwent radical surgery in contrast to half of those treated laparoscopically. We feel this largely reflects our

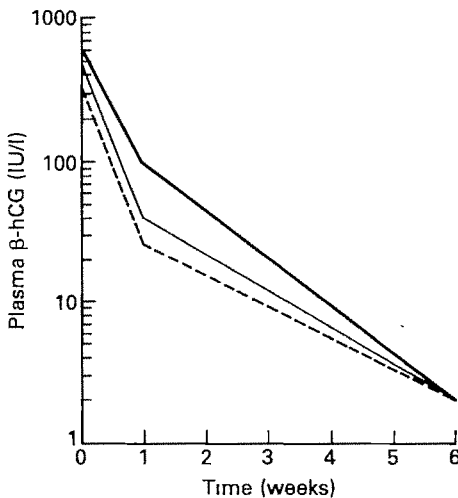


Fig. 1. Median plasma human chorionic gonadotrophin (β -hCG) concentrations before and after videopelviscopy and laparotomy for ectopic pregnancy (Salpingotomy, —; Salpingectomy, —; Laparotomy, —).

Table 4. Cost comparison of videopelviscopy and laparotomy for 20 patients in each treatment group without per- and post-operative complications

	Videopelviscopy		Laparotomy	
Accommodation (£)	248.00	(160-480)	808.00	(480-1280)
Investigations (£)	45.89	(19.37-49.37)	41.91	(18.00-55.37)
Operating theatre (£)	270.00		270.00	
Drugs and iv fluids (£)	8.38	(2.54-13.64)	17.57	(7.48-42.70)
Statutory sickness payment (£)	130.25	(26.05-338.65)	266.51	(182.35-390.75)
Overall costs (£)	702.52	(477.96-1151.66)	1403.99	(957.83-2038.82)*

* $P < 0.001$

Results are mean (range) values

preference for conservative intervention whenever clinically appropriate, but another explanation may be the observation that tubal and ovarian surgery appears to be associated with less haemorrhage when the abdomen is not opened (Semm 1987). While our study was not designed to address the relative merits of conservative and radical surgery, it is worthy of comment that tubal conservation does not increase the recurrence risk of ectopic gestation (DeCherney & Kase 1979, Hallatt 1986). Indeed, tubal salvage may even be indicated in women with a solitary tube as subsequent rates of intrauterine pregnancy can be relatively high, although at the expense of an increased ectopic risk (Langer *et al.* 1987; Oelsner *et al.* 1987). These data are in accord with our results of 'normal' hysterosalpingograms in 15 of 20 women after conservative surgery, as well as with histopathological evidence that ampullary pregnancies, the most frequent site for extra-uterine implantation, are usually intraluminal with little disruption to the tubal wall (Dubuisson *et al.* 1986, Senterman *et al.* 1988).

Surgical techniques apart, a major advantage of videopelviscopic surgery over laparotomy lies

with the patients' quick and uncomplicated recovery and the associated financial savings; indeed outpatient management of ectopic pregnancies has been described (Loffer 1987). The economic implications of avoiding open surgery were first quantified by Levine (1985), who in a series from the USA showed a saving of 79% for drugs and other medical supplies, and 49% in overall hospital costs. Our analysis within the National Health Service in the UK produced remarkably similar results, with savings of 69% for accommodation, 52% for drug costs, and 51% for statutory sickness payments compared with laparotomy. All in all, videopelviscopy lead to an overall reduction of costs by 50%, with savings for the health and social services of £701 per patient. Comparing this figure to the £10 000 or so necessary for a basic set of videopelviscopic instruments including a videocamera clearly proves the cost effectiveness of such investment in medical technology.

This study shows that most women with ectopic pregnancy who are not shocked can be managed without open surgery. Videopelviscopy is associated with considerable benefits to the patient as well as major savings to the health and

Table 5. Summary of the main results of the current study and those of Brumsted *et al.* (1988)

	Current study		Brumsted <i>et al.</i>	
	Laparoscopy	Laparotomy	Laparoscopy	Laparotomy
Number of procedures	65	27	25	25
Gestation (weeks)	7.0	6.6	6.8	6.8
Ampullary implantation	85%	77%	88%	88%
Tubal wall intact	75%	74%	76%	76%
Salpingotomy	45%	7%	28%	28%
Salpingectomy	43%	74%	60%	60%
Procedure time (min)	55.3	51.1	77.5	103.6
Hospital stay (days)	1.7	5.2	1.3	3.9
Return to normal activities (weeks)	1.5	3.3	1.2	3.7
Return to work (weeks)	2.5	5.7	Not stated	

social services, and this is not at the expense of prolonged operating times. As most practising gynaecologists are already familiar with diagnostic laparoscopy, little extra training would be required to master the necessary surgical techniques. Once learned, the skills of videopelviscopy can be applied to many other gynaecological conditions traditionally managed by laparotomy (Semm 1987). The training and equipment required are relatively minor compared to the potential benefit to our patients that would be afforded by a widely available videopelviscopy service.

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Audit of workload in gynaecology: analysis of time trends from linked statistics

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Abstract

Objective—To report on trends in workload patterns in gynaecology using linked statistical data.

Design—Retrospective analysis of linked abstracts of hospital inpatient and day-case records for patients treated in the National Health Service in gynaecology.

Setting—Six health districts in the south of England covered by the Oxford record linkage study.

Subjects—Records for hospital admissions to gynaecology (excluding obstetric admissions) from 1975 to 1985.

Measurement and main results—Inpatient episodes increased by 23.5% and day case episodes increased by 13.1%. More people treated contributed about 90% and increased readmissions contributed about 10% to the increase in workload. The workload was decreased by strike action in 1975 and 1981-2. Average length of stay decreased substantially and consistently over the 11 years. Emergency readmissions increased annually by an average of 2.7%. Admission rates in 11 groups of surgical procedures accounting for 85% of all gynaecological inpatients are reported, and increases occurred in 10 of the 11 groups. For example, average increases in annual admission rates were 1.0% for sterilization, 1.9% for legal abortion and 8.2% for biopsy of the cervix, the rate for dilatation and curettage decreased by 1.4%.

Conclusions—The increase in admission rates in gynaecology was almost entirely due to increases in numbers of people treated. The rise would have been even greater if the increase in private patients had been considered. The increase may reflect increased expectations on the part of patients and their doctors, advances in technology and increased bed availability due to declining lengths of stay.

The White Paper 'Working for Patients' has stressed the importance of measuring, auditing and contracting for workload (Secretaries of State for Health, Wales, Northern Ireland and Scotland 1989). Clinicians are increasingly being called upon to assume managerial control of,

and responsibility for, the services in which they work. There is, therefore, increasing interest in levels and patterns of care and, in particular, in numbers of patients admitted, numbers of episodes per person, average lengths of stay, emergency readmissions, and time trends in

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admission rates for clinical conditions and surgical procedures

Clinician-managers are realizing that audit enables them to assess the efficiency of local services, particularly if the service is undergoing technological change. Indeed, the impact of current changes in gynaecology is likely to be dramatic: use of endometrial resection and laser ablation of the endometrium for controlling menorrhagia; future use of antiprogesterone agents (the 'abortion pill') for unwanted pregnancy; use of in vitro fertilization for treating infertility; use of hysteroscopy for diagnostic purposes and improved imaging techniques such as ultrasound and magnetic resonance. These changes will affect the pattern of care required by patients, increasing the importance of auditing workload.

Routinely collected statistics show that there has been a consistent rise in hospital admission rates of about 2% per annum across all specialties in the acute sector in England (Goldacre *et al.* 1988). There are limitations, however, in using routine information systems in the National Health Service to understand patterns of workload because routine data are episode-based and unlinked: thus two or more admissions for the same individual cannot be distinguished. The Oxford Record Linkage Study has been used to relate workload statistics to the care of individuals by linking together successive episodes relating to the same individual (Acheson 1987).

This report is for gynaecology from a series of studies being undertaken, one in each specialty, to examine past trends in workload in each specialty using linked data

Subjects and methods

The Oxford Record Linkage Study is a collection of abstracts of hospital inpatient records (including day cases), birth registrations and death certificates. The data are collected in such a way that records relating to the same individuals can be linked together and analyzed to produce unduplicated counts and time-sequenced information about numbers of people in receipt of care (Acheson 1987). The analyses presented here relate to residents of the six districts of the Oxford Regional Health Authority covered by data collection between 1975 and 1985.

First, we analyzed trends in episode-based and person-based admission rates to gynaecology (excluding obstetric admissions).

Second, we analyzed patterns of readmission for individuals discharged from gynaecology. A readmission was defined as the first subsequent hospital episode (excluding transfers) to any specialty for a patient within 28 days of discharge from gynaecology. The method used has been discussed elsewhere (Henderson *et al.* 1989a). Third, average lengths of stay and total days spent in hospital by each individual in each year in gynaecology were calculated. The latter calculation was based on the sum of the lengths of stay of all the gynaecology episodes experienced by an individual in each calendar year. Finally, clinical caseload for the specialty is described using the short list of surgical procedures in the Office of Population Censuses and Surveys' Classification of Surgical Operations (OPCS 1975). Chi squared tests for trend were used to test the significance of changes over the time between 1976 and 1985.

Results

Person-based gynaecological admission rates for females in 1975 and 1985 are shown in Fig. 1 in quinquennial age bands. Admissions rates are low in the youngest age-groups, peak in the fertile years and decline after the menopausal years. There was a substantial increase in person-based admission rates between 1975 and 1985 in virtually every age-group.

Trends over time in person-based, age-standardized admission rates in gynaecology are shown in Fig. 2. There was an upward trend which was not entirely consistent, because of a decline in admission rates from 1981 to 1983.

Episode-based and person-based admissions are compared as the mean number of episodes per person in each year in 1976 and 1985 (Table 1). Because 1975 was an atypical year due to industrial action, as discussed below, data for 1976 were used in this table. The data illustrate the extent to which routine episode-based health service statistics were inflated by multiple admissions for the same person: in fact, in gynaecology, there was only a small inflationary factor with the greatest number of episodes per person in women aged 60 years and over. For example, in 1976 there was a total of 19 310 inpatient and day case admissions for 16 885 people, while in 1985, there was a total of 26 368 inpatient and day case admissions for 23 426 people. The number of people admitted as

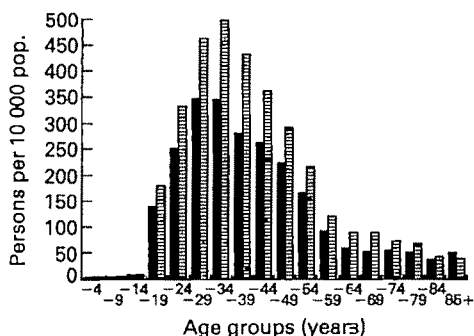


Fig. 1. Person-based gynaecological admission rates, by quinquennial age bands, for females in the Oxford Region in 1975 (■) and 1985 (▤)

inpatients and day cases in gynaecology increased by 38.7% in this period while the number of inpatient and day-case episodes increased by 36.6%. The increases for inpatients (excluding day cases) were 25.0% and 23.5% respectively. The fact that the increase in numbers of people treated was a little greater than the increase in episodes of treatment reflects the slight decrease in the number of hospital episodes per person hospitalized over the time period.

Two measures of time spent in hospital are presented in Table 2. Average length of stay per episode, the conventional measure available from routine statistics, is shown and compared with the total time in hospital per individual, taking account of multiple episodes per person. A consistent decrease in both measures over the 11 years is apparent.

Concern is sometimes expressed that falling lengths of stay might be accompanied by an increase in emergency readmissions. We there-

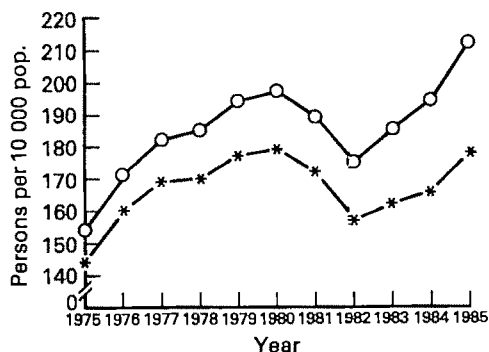


Fig. 2. Age-standardized person-based gynaecological admission rates for females in the Oxford Region, 1975-85. *—* inpatients; ○—○ inpatients plus day cases

fore analyzed the percentage of patients who experienced emergency admissions (to any specialty) within 28 days following treatment in gynaecology (Fig. 3). There was a clear and consistent increase in emergency readmissions from 1978 to 1985 with a statistically significant average annual increase of 2.7% (95% confidence interval 1.84 to 3.49, $P < 0.001$) over the 11-year period.

Trends between 1976 and 1985 in admission rates for selected surgical procedures are shown in Table 3. Only those gynaecological operations which underwent a significant change in workload over time have been included: the 11 groups of surgical procedures described accounted for 85.0% of the total number of people admitted to gynaecology. Changes over time ranged from an average increase of 8.2% per annum in admission rates for biopsy of the cervix to an average decrease of 1.4% per annum in rates for dilatation and curettage.

Discussion

The increases in hospital admissions for gynaecological treatment between 1975 and 1985, particularly in the fertile age range, are striking. These trends confirm the clinical impression that

Table 1. Number of episodes per female admitted to hospital for gynaecology in the Oxford region in 1976 and 1985

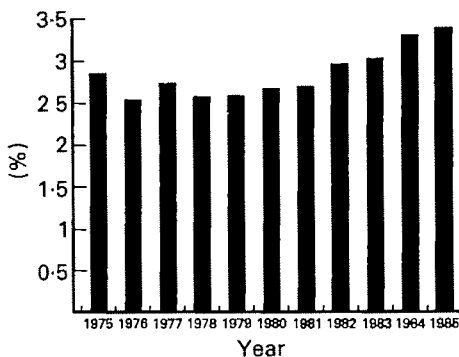
Age group	Episodes per person hospitalized	
	1976	1985
0-4	1.00	1.00
5-9	1.00	1.04
10-14	1.09	1.10
15-19	1.09	1.11
20-24	1.13	1.15
25-29	1.13	1.14
30-34	1.15	1.13
35-39	1.15	1.10
40-44	1.16	1.09
45-49	1.15	1.11
50-54	1.15	1.11
55-59	1.15	1.14
60-64	1.24	1.17
65-69	1.18	1.21
70-74	1.20	1.18
75-79	1.28	1.20
80-84	1.23	1.14
85+	1.23	1.21
Total	1.14	1.13

Table 2. Average lengths of stay in hospital and average total days in hospital per year in gynaecology

Year of admission	Average length of stay per episode (days)	Average total days in hospital per person
1975	5.1	5.8
1976	4.5	5.2
1977	4.3	4.9
1978	4.0	4.5
1979	3.8	4.2
1980	3.5	4.0
1981	3.6	4.0
1982	3.5	4.0
1983	3.4	3.8
1984	3.2	3.6
1985	3.0	3.4
Mean	3.8	4.3

there has been a real rise in referrals. Laparoscopy, colposcopy and conservative surgery for intraepithelial neoplasia, and many other innovations have increased the perceived benefit of referral (Noble 1985). Perhaps women with gynaecological problems and their general practitioners, aware of these innovations in the specialty, are less anxious than before about referral to specialist care. Our data underestimate the admissions for residents of the six districts because we have no comparable data on private patients or on residents treated outside the districts.

The use of day case surgery has increased, as illustrated in Fig. 2. As reported elsewhere (Henderson *et al.* 1989b), three gynaecological operations—termination of pregnancy, sterilization and dilatation and curettage—were increasingly undertaken on a day case basis

**Fig. 3.** Emergency gynaecological readmission rates within 28 days of discharge for females in the Oxford Region, 1975-85

during the period although the use of day case care for patients in these categories was still well under 50% by 1985. Some regions have set targets for day care in their strategic plans: for example, in the Oxford Region it is proposed that 25% of hospital admissions in the acute services could be undertaken on a day care basis by 1994 (Oxford Regional Health Authority 1984).

During 1975-85 hospital admission rates in gynaecology increased in most years. The troughs shown in Fig. 2 parallel industrial action in 1975 and 1981-2 (Goldacre *et al.* 1987). 1975 was the first year in which major industrial action was taken by doctors since the establishment of the National Health Service and this resulted in a decline in workload. In 1981-2 other industrial action reduced elective inpatient admissions. The general trend of admission rates in gynaecology was nonetheless upward. Speculation over the rise in episode based rates of hospital admissions nationally has fuelled debate about whether each year more people than ever before have received hospital care, or whether there has been an increase in multiple admissions per individual (Goldacre *et al.* 1988). In the case of gynaecology in the Oxford region, an increase in the numbers of people treated contributed about 90% and an increase in multiple admissions per individual contributed about 10% to the increase in workload. Many gynaecological patients over 60 years of age are treated for malignant neoplasms of the cervix, uterus and ovary. These diseases tend to be managed in multiple episodes which probably explains, at least in part, why the greatest number of episodes per person occurred in women in this age group. Overall, there was a decrease in episodes per person over the time period. This is a trend not seen in other specialties and may indicate a change in the balance of type of treatment, for example, an increase in operations for benign conditions which only involve one admission.

The data in Table 2 confirm that lengths of stay per episode and the total number of days an individual stays in hospital each year have both decreased in gynaecology. Improved surgical techniques, prophylactic antibiotics, better cooperative care with general practitioners, improved liaison with medical and nursing community services and trends towards greater efficiency and economy in the use of resources have all probably worked towards shortening duration of stay (Noble 1985).

Table 3. Trends in surgical procedures in gynaecology in the Oxford region 1976–1985 inpatients and day cases expressed as rates per 10 000 women

OPCS code short list	Surgical procedure	Person-based admission rate		Average annual % change	95% Confidence interval
		1976	1985		
080 (part)	Biopsy of cervix	2.49	6.00	+8.2	+6.93 to +9.51
038	Operations on abdominal wall, peritoneum and mesentery (includes laparoscopy)	8.54	15.89	+6.5	+5.83 to +7.13
085	Operations on vulva	1.75	3.26	+6.5	+5.01 to +8.05
082	Colporrhaphy	3.70	5.41	+3.3	+2.23 to +4.42
076–077	Division and ligation of oviducts, other operations involving oviduct	17.90	26.82	+1.0	+0.58 to +1.44
080 (part)	Excision of lesion of cervix	1.89	3.30	+3.1	+1.62 to +4.53
092	Post-natal or post-abortion operations	16.15	22.41	+2.7	+2.74 to +3.24
087	Termination of pregnancy (excluding hysterotomy)	20.75	24.86	+1.9	+1.45 to +2.41
078	Hysterectomy	22.37	25.92	+0.5	+0.07 to +0.97
080 (part)	Dilatation and curettage	44.79	42.98	–1.4	–1.77 to –1.10

There has been speculation in the health service that the increase in admission rates and the decline in lengths of stay may be connected by an increase in emergency readmissions. Emergency readmission rates in patients discharged from gynaecology, although low, have increased slightly in the Oxford Region. It is difficult to interpret the rise. It could, for example, reflect discharge too early from care in the first admission, or it could be a consequence of an increase in treatment of diseases which require subsequent admission. More detailed studies than ours would be needed to clarify this.

The increase in admission rates for biopsy of cervix reflects increased concern about disease of the cervix, decreased patient anxiety regarding the procedures they are offered owing to advances in technology and an increase in the population of women covered by screening procedures. Hysterectomy rates increased only slightly between 1975 and 1985. This is comparable with the increase seen nationally (Coulter *et al.* 1988). During the time period covered by the data in this study, endometrial resection and endometrial ablation were experimented with in the United States. They are now established pro-

cedures for the treatment of menorrhagia, a common indication for hysterectomy in the United Kingdom. Whereas a hysterectomy generally requires a 7-day stay in hospital, a major operation and up to 2 months recovery time, these new procedures can be performed with an overnight hospital stay, or even occasionally as day cases.

The availability of linked records means that patterns of hospital care can be analyzed in relation both to episodes of hospital care and to individuals receiving such care. Both indices are important. The White Paper 'Working for Patients' has stressed the importance of measuring, auditing and contracting for workload. Managers and clinicians will be interested in episode-based patterns of admission as measures of 'units' of treatment; and clinicians and epidemiologists will be interested in the numbers of individual patients treated. Implementation of the recommendations of the National Steering Group on Health Services Information (Department of Health and Social Security 1982), chaired by Mrs E. Körner, should mean that authorities throughout the country will be able to monitor workload in similar ways to that reported in this paper.

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Pretreatment of the primigravid uterine cervix with mifepristone 30 h prior to termination of pregnancy: a double blind study

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Abstract

Objective—To determine the effect of the antiprogesterone mifepristone (RU 486) on cervical resistance before first trimester termination of pregnancy.

Design—Prospective double blind randomized placebo controlled study.

Setting—Department of gynaecology in a university teaching hospital, Sheffield.

Subjects—80 Primigravid women >18 years of age, undergoing termination of pregnancy at between 7 and 13 weeks gestation

Interventions—A single dose of 600 mg of mifepristone or placebo given orally 30 h before termination of pregnancy under general anaesthesia

Main outcome measures—Cervical resistance to dilatation.

Results—Pretreatment with mifepristone significantly reduced the amount of force required to dilate the cervix to 10 mm. In comparison with placebo, the mean sum of the peak forces obtained with dilators 4 to 10 mm was reduced from 84.3 N (SD 29.7) to 46.0 N (SD 26.7). Two women in the treated group had a cervical resistance of >100 N compared with nine women in the placebo group (RR 0.18, 95% CI 0.04-0.89). The 8 mm dilator could be passed with less than 5 N force in 16 women (43%) in the treated group compared with none in the placebo group. Women in the active treatment group had more preoperative pelvic pain and vaginal bleeding but less postoperative pain.

Conclusion—Mifepristone significantly reduces cervical resistance in the first trimester of pregnancy and produces minimal side effects.

Before surgical termination of pregnancy many gynaecologists prefer to pretreat the cervix of certain 'at risk' women with prostaglandins or intracervical tents to facilitate dilatation. Such treatments may not be well tolerated by the women as prostaglandins can cause bleeding,

pelvic pain and gastrointestinal side-effects (Christensen *et al.* 1982) whilst intracervical tents can be difficult and sometimes painful to insert (Welch *et al.* 1984).

There is increasing evidence that the antiprogesterone mifepristone (RU 486) can dilate the cervix of pregnant women (Cabrol *et al.* 1985; Couzinet *et al.* 1986). Trials to assess the effect of mifepristone on the cervix in the first trimester have used subjective assessments (Durlot *et al.* 1988; WHO 1990) or have treated only a small number of women and of mixed parity (Gupta & Johnson 1990). In the most recent study (WHO 1990) four different doses of mifepristone were given twice at 24 and 12 h before vacuum aspiration. Such a regimen is unlikely to be conven-

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ient in current clinical practice with the emphasis on day care surgery.

We report here a double-blind placebo controlled trial which assessed objectively the effect of a single dose of 600 mg mifepristone given 30 h before first trimester termination of pregnancy in nulliparous women.

Subjects and methods

All the women in the study were primigravidae, over the age of 18 and between 7 and 13 weeks pregnant, as assessed by the date of their last menstrual period or ultrasound scan. They all fulfilled the criteria set out in the 1967 Abortion Act for a legal abortion and gave written informed consent which specifically stated that once the trial medication had been administered they were advised to continue with the termination of pregnancy. The protocol was approved by the local ethics committee.

Women with clinically significant cervical pathology or any previous operations involving dilating the cervix were excluded, as were those with signs and symptoms of miscarriage. Women were also excluded from the trial if they had been treated in the last 4 weeks with other medications likely to affect the outcome of the pregnancy, interfere with prostaglandin synthesis or natural hormone production or had been treated in the past 6 months with glucocorticoids.

The trial was double blind and randomization was computer generated in blocks of 10. Eighty women were assigned to receive either 600 mg of mifepristone (Roussel Laboratories, Ltd) as 3 × 200 mg tablets or a matching placebo. Women attended the ward 30 h before the planned termination. The three tablets were swallowed with 150 ml water and the women were observed for 2 h. During this time side-effects were noted and pulse, blood pressure and temperature recorded. Further enquiries into side-effects

were made when the women returned the next day.

All terminations of pregnancy were performed as day cases under general anaesthesia. Ten units of oxytocin were injected intravenously with induction of anaesthesia.

Before evacuation of the uterus, the resistance of the cervix to dilatation was objectively assessed using a series of tapered dilators attached to a force-sensing handle. The sum of the peak forces for dilators 4–8 (4–10 mm) was used as a measurement of cervical resistance (Kenyon *et al.* 1988). The internal diameter of the cervix before dilatation was taken to be the diameter of the largest dilator that could be passed with a force of <5 Newtons (N).

After evacuation, the total aspirate was recorded as a measure of blood loss. All women were asked to attend for follow-up at 7 and 28 days after operation.

Previous studies had shown that the mean cervical resistance of untreated women was 80 N (SD 30). A reduction to half this value would be clinically highly significant. Forty women in each group would demonstrate such a difference with a power of >95% and an α error of 5%.

The Mann-Whitney *U* test was used to test for difference between the means. Relative risks (RR) and 95% confidence interval (95% CI) are stated where required.

Results

Of the 80 women recruited two withdrew after having taken the trial medication because they wished to continue with the pregnancy. One had taken placebo and so was reassured accordingly whilst the other had had the active drug. She had vomited within 2 h of taking the treatment and saw at least one partially digested tablet in the vomitus. She and her partner were counselled appropriately. She went into spontaneous

Table 1. Characteristics of women given 600 mg mifepristone or placebo 30 h before termination of pregnancy

Characteristic	Mifepristone (<i>n</i> = 40)	Placebo (<i>n</i> = 40)
Age (years)	22.0 (3.45)	21.0 (2.81)
Gestation (days)	71.9 (7.93)	68.7 (9.32)
Drug to termination interval (h)	29.5 (0.53)	29.6 (0.46)

Results are mean (SD) values.

Table 2. Cervical resistance (measured as the sum of the peak forces for dilators 4 to 8) 30 h after treatment with 600 mg mifepristone or placebo before termination of pregnancy

Force required to dilate cervix (N)		
Mifepristone (<i>n</i> = 37)	Placebo (<i>n</i> = 37)	Difference between means
Mean (SD)	Mean (SD)	Difference (95% CI)
46.01 (26.75)	84.31 (29.45)	38.3 (24.9 to 51.7)

Table 3. Cervical internal diameter 30 h after pretreatment with 600 mg of mifepristone or placebo before termination of pregnancy

Diameter (mm)	Mifepristone (<i>n</i> = 37)			Placebo (<i>n</i> = 37)			Relative risk (95% CI)
	<i>n</i>	Cum	Cum%	<i>n</i>	Cum	Cum%	
<5	4	37	100.0	12	37	100.0	
6	8	33	89.2	14	25	67.6	3.96 (1.84 to 13.74)
7	9	25	67.6	11	11	29.7	4.92 (1.84 to 13.20)
8	9	16	43.2	0	0	0	
9	5	7	18.9	0	0	0	
10	2	2	5.4	0	0	0	

Cum = cumulative number, Cum% = cumulative per cent

labour at 41 weeks gestation and gave birth to a normal female infant, weighing 3585 g, with normal external genitalia

The characteristics of the two groups of women are shown in Table 1. There were no significant differences in the age or gestation between the two groups. In the 30 h following treatment 17 women in the treated group complained of mild abdominal pain compared with four in the control group (RR 6.76; 95% CI 2.00–22.65). Only one woman in the treated group had taken paracetamol whilst two in the placebo group had required analgesia. Two women in the treated group and none in the control group had had some mild vaginal bleeding. The cervical resistance was not ascertained in four women due to computer failure in two and to operator error in the other two. Pretreatment with mifepristone significantly reduced the amount of force required to dilate the cervix to 10 mm (Table 2), all dilators were easier to insert in the treated group, resulting in a 45% reduction in the total force required. Nine women in the placebo group had a cervical resistance value of >100 N compared with two in the treated group (RR 0.18; 95% CI 0.04–0.89). An internal diameter of ≥ 8 mm was found in 16 women (43%) in the treated group compared with none in the untreated group (Table 3). There was no

difference between the women who had complained of pelvic pain and those who had no pain in the length of gestation (71.6, SD 8.42 vs 70.5, SD 9.23 days amenorrhoea) or the amount of force required to dilate the cervix (48.8 SD 33.4 vs 46.7 SD 24.0 N).

There were no immediate operative complications. The mean loss was lower in the mifepristone treated group (146.5, SD 84.6, range 50–550 ml) than in the placebo group (173.8, SD 115.6, range 50–600 ml) but the difference was not clinically or statistically significant ($P = 0.214$).

In the immediate postoperative period there were no differences in the symptoms complained of by the women (Table 4) and they were all returned home within 6 h.

Thirty-one women from the treated group and 32 from the placebo group attended for follow-up 7 days later. Significantly fewer of those who had taken mifepristone complained of pelvic pain and they tended to have used less analgesia (Table 5). There was no difference in other symptoms or the amount of bleeding as assessed by the women.

Table 4. Distribution of symptoms after termination and before discharge in women pretreated with mifepristone or placebo

Symptom	Mifepristone (<i>n</i> = 40)	Placebo (<i>n</i> = 40)	Relative risk (95% CI)
Pelvic pain	24 (61%)	22 (56%)	1.24 (0.50–3.03)
Headache	10 (26%)	6 (15%)	1.90 (0.61–5.87)
Nausea	1 (3%)	1 (3%)	1.00

Table 5. Distribution of symptoms 7 days after termination of pregnancy in women pretreated with mifepristone or placebo

Symptom	Mifepristone (<i>n</i> = 31)	Placebo (<i>n</i> = 32)	Relative risk (95% CI)
Pelvic pain	10 (32%)	19 (59%)	0.33 (0.12–0.91)
Headache	6 (19%)	6 (19%)	1.04 (0.30–3.67)
Nausea	1 (3%)	0	
Bleeding			
Mild	18	20	
Moderate	7	6	
Heavy	6	4	

One woman in the placebo group was admitted after 7 days with pain, vomiting and moderate vaginal loss. She was taking tetracycline because an endocervical swab taken before termination had shown the presence of *Chlamydia trachomatis*. There was no evidence of retained products and her symptoms settled after 36 h.

One woman in the mifepristone treated group was admitted again at 14 days after the abortion with heavy vaginal bleeding for 2 days. Retained products of conception were seen on ultrasound and she underwent evacuation of the uterus.

There were no differences between the two groups when assessed at 28 day follow-up.

Discussion

The number of first trimester pregnancies terminated by surgical dilatation and suction evacuation continues to increase in England and Wales (Office of Population Censuses and Surveys). It has been shown that difficulty in cervical dilatation is related to cervical trauma, uterine perforation and incomplete evacuation of the uterus (Grimes & Cates 1979) which are important complications of early pregnancy termination. The present study has shown that treatment with oral mifepristone can soften and partially dilate the cervix when given 30 h before mechanical dilatation. The force required to dilate the cervix was similar to that found when women were pretreated with prostaglandins (Kenyon & Stewart. Unpublished data).

Previous studies using prostaglandins or cervical tents to pretreat the cervix have shown a significant occurrence of side-effects such as vaginal bleeding, gastrointestinal upset and abdominal pain (Chen & Elder 1983; Welch *et al.* 1984). Durlot *et al.* (1988) treated a series of women with 100 mg of mifepristone twice daily for 48 h and found that 62% experienced vaginal bleeding and 7% passed products of conception. In our study only 4% of the women reported bleeding and this was very slight. This difference may be related to the different time scale for treatment. Compared with placebo, mifepristone was associated with more pelvic pain before surgery but this did not appear to be clinically significant when judged by the analgesia taken by women. No other side-effects attributable to treatment with mifepristone were noted and this is a considerable advantage over other currently available therapies. The relative lack of pain during the 7 days after the operation in the

women who had received mifepristone is interesting and has not been reported by other authors. The oral route of administration may also be considered by some to be a benefit.

A reduction in blood loss after termination has been noted in women pretreated with prostaglandins (McKenzie & Fry 1981). This has been assumed to be due to the effect of prostaglandins on uterine contractility. No such reduction was noted in this study. This may suggest, if the antiprogesterone mediates its effect on the cervix through the action of endogenous prostaglandins, that these have a much less potent effect on uterine contractility than the exogenous prostaglandins used in other studies. The comparative lack of postoperative pain in the treated group may be associated with the mode of action of the drug. We are currently investigating the effect of mifepristone on the structure of the cervix.

Our study suggests that mifepristone is a useful adjunct to surgical termination of pregnancy and may prove to be more acceptable than the use of prostaglandins.

Acknowledgments

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Follicular development in spontaneous and stimulated cycles in women with minimal-mild endometriosis

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Abstract

Objective—To study follicle development in women with minimal-mild endometriosis

Design—In women with endometriosis a spontaneous ovulatory cycle was compared with two subsequent cycles in which either clomiphene or clomiphene and FSH were given to stimulate folliculogenesis. Spontaneous cycles in women with tubal infertility provided a comparison group.

Setting—Infertility clinic, Aberdeen Maternity Hospital.

Subjects—17 women with minimal-mild endometriosis and 10 women with tubal infertility.

Interventions—The women with endometriosis were treated with 150 mg clomiphene citrate from days 2 to 6 in one cycle and in a subsequent cycle with 150 mg clomiphene citrate on days 2 to 6 plus 75 iu FSH daily thereafter.

Main outcome measures—Follicular size measured daily using ultrasound. Serum FSH estimated on days 5 and 7 and then daily.

Results—Spontaneous follicular growth in the women with endometriosis was similar to that in the women with tubal infertility. Follicular development began earlier in cycles with clomiphene/FSH and the leading follicle reached 16 mm 2 days sooner but the rate of growth was similar whether or not either regimen of stimulation was used.

Conclusion—Follicular growth is not impaired by minimal-mild endometriosis. Infertility with this condition cannot be explained by altered follicular growth or responsiveness

Although minimal-mild endometriosis is frequently diagnosed among infertile women, the relation between this disorder and subfertility is ill-defined (Mahmood & Templeton, 1989; 1990). Various abnormalities such as a defective luteal phase and a biphasic LH surge (Williams *et al.* 1986), a higher incidence of luteinized

unruptured follicle syndrome (Hamilton *et al.* 1985, Dmowski *et al.* 1986) and an occult ovulatory dysfunction (Arumugam *et al.* 1989, Tummon *et al.* 1988; Eissa *et al.* 1987) have been described. However, data on folliculogenesis in patients with endometriosis are very limited. Recently Doody *et al.* (1988) reported a slower follicular growth rate in women with endometriosis than in normal women and this defect could not be corrected with the use of clomiphene citrate. Follicle stimulating hormone (FSH) is important in follicular recruitment and selection during spontaneous and hyperstimulated cycles (Hodgen 1982; Kern *et al.* 1985; Messinis *et al.* 1986). Although clomiphene combined with FSH has been reported to accelerate follicle growth in patients with tubal infertility (Temple-

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ton *et al.* 1986) the effect of such a treatment on folliculogenesis in patients with endometriosis has not been investigated.

The purpose of the present study was to investigate follicular development in women with minimal-mild endometriosis during spontaneous cycles and in cycles hyperstimulated with clomiphene with or without FSH.

Subjects and methods

The study included 27 women. The first group comprised 17 women with regular spontaneous menstrual cycles and primary infertility who had had minimal-mild endometriosis diagnosed at laparoscopy. The median AFS score (The American Fertility Society 1985) was 7 (range 2–10). They were between 23 and 35 years of age (median 30 years) and had a duration of infertility of 3.5–7 years (median 5 years). All had ovulatory midluteal phase serum progesterone values (≥ 30 nmol/l) and normal prolactin values (< 500 mIU/l) for at least the two cycles before entering the study. Each woman was studied in three different cycles: (i) spontaneous cycle; (ii) induced with clomiphene; (iii) induced with clomiphene plus pure FSH. Between the second and third cycles, the women had a break of at least one month. The second group included 10 volunteer women with primary infertility due to bilateral tubal occlusion who were recruited as controls. They were between 27 and 35 years of age (median 31 years) and had a duration of infertility from 3 to 7 years (median 5 years). They all had ovulatory midluteal phase progesterone and normal serum prolactin values as above. These women were studied only during a spontaneous cycle and had a total of 12 cycles monitored (two women had two cycles each). The endocrine profile during these cycles was similar to that observed during the spontaneous cycles in the endometriosis group (data not shown).

Study design

During the 29 spontaneous cycles monitored, all the women were scanned daily (Diasonic DRF200; 7.5 MHz vaginal probe; Diasonic Sonotron, Bedford) from cycle day 5. Blood samples (08.00 hours) were taken on cycle days 5, 7 and daily thereafter. Once the dominant follicle measured > 16 mm, blood samples were obtained every 6 h for luteinizing hormone (LH)

measurement (data not shown). Each follicle was measured in two planes and the measurements were repeated and photographed. For each follicle, a diameter was calculated as the mean of four measurements. All these women had follicular aspiration and oocyte recovery performed 32 h after the onset of the LH surge and the results have been described elsewhere (Mahmood *et al.* 1991).

During the second cycle in the endometriosis group, the women were treated with clomiphene, 150 mg daily, from cycle days 2 to 6. Daily blood samples were taken and ovarian ultrasound scans were recorded starting on cycle day 5.

During the third cycle in the endometriosis group, the women were treated with clomiphene, 150 mg daily, from cycle days 2 to 6 plus 'pure' FSH (Metrodin, Serono Laboratories, UK) intramuscularly, one ampoule (75 iu FSH per ampoule) on cycle days 4 and 5 and two ampoules/day thereafter. Blood samples were taken on cycle days 2, 4, 5 and daily thereafter. Ovarian ultrasound scans were recorded daily starting on cycle day 5.

During the second and third cycles, 5000 iu human chorionic gonadotrophin (hCG) was given when the leading (largest) follicle exceeded 18 mm in diameter. Women in the second cycle had direct intraperitoneal insemination and in the third cycle gamete intrafallopian transfer 34 h after the hCG injection (data not shown). None of the women in the stimulated cycles had evidence of the onset of an endogenous LH surge (Messinis *et al.* 1985) up to the time of hCG administration. Ethical approval for these studies was given by the Joint Ethics Committee of Grampian Health Board and University of Aberdeen.

Hormone assays

FSH was measured by monoclonal antibodies in an immunoradiometric assay (IRMA; Serono Diagnostics) and the results expressed as mIU/ml of standards of human pituitary FSH (WHO 2nd IRP 78/549). The lower limit of detection for FSH was 1.0 iu/ml. Inter- and intra-assay coefficients of variation were 7.9% and 7.8% respectively.

Statistical analysis

For data analysis in the endometriosis group,

each woman acted as her own control for comparison with each of the two stimulated cycles. Statistical analysis of the results within the groups used the paired *t* test. The data of these three subgroups in the endometriosis group were further compared by analysis of variance. The data from women with tubal infertility were compared with data from three cycles in women with endometriosis using an unpaired *t* test. (Minitab statistical package, Statistics Department, Pennsylvania University).

Results

In this study, the cycle day on which the leading follicle reached or exceeded 18 mm in diameter was taken as a reference point and is referred to hereafter as day 0. This reference point was selected for two reasons, first because there was no endogenous LH surge in either of the two stimulated cycles and hCG was injected when the leading follicle was ≥ 18 mm in diameter; and

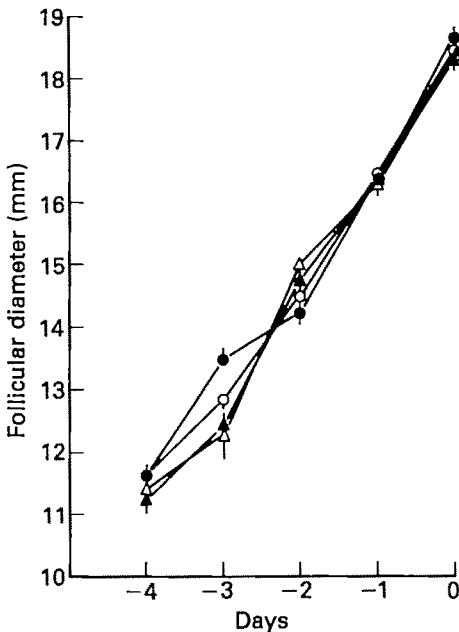


Fig. 1. Rate of growth of the leading (largest) follicle estimated by ultrasound during the mid- to late follicular phase in 17 normally cycling women with minimal-mild endometriosis (spontaneous cycles Δ , clomiphene cycles $\circ$, clomiphene plus FSH cycles $\bullet$). Comparison with 12 spontaneous cycles in women with tubal infertility ($\blacktriangle$) (Mean $\pm$ SEM). Day 0 is the day on which the leading follicle reached or exceeded the size of 18 mm in diameter.

second because in agreement with previous data (Templeton *et al.* 1986), in the present study the endogenous LH surge in the spontaneous cycles started when the leading follicle was at least 18 mm in diameter.

In the endometriosis group the mean duration of the follicular phase, from the first day of the cycle to day 0, was 14.5 (SEM 0.7) days in the spontaneous cycles, 12.5 (SEM 1.0) days in the clomiphene stimulated cycles and 10.5 (SEM 0.5) days in the clomiphene plus FSH stimulated cycles. The corresponding duration in the tubal infertility group was 14.0 (SEM 0.5) days. There was no significant difference in the duration of the follicular phase of the spontaneous cycles between the endometriosis and tubal infertility groups, nor between the spontaneous and clomiphene stimulated cycles, nor between the clomiphene only and clomiphene plus FSH stimulated cycles, but there was a significant difference between the spontaneous cycles and the clomiphene plus FSH stimulated cycles ($P < 0.01$).

The mean number of follicles > 15 mm on day 0 was higher in the clomiphene plus FSH cycles (5.3, SEM 0.5) than in the clomiphene only cycles (3.4, SEM 0.2) ($P < 0.01$).

The size of the leading follicle on days -4 to 0 did not differ significantly between the three cycles in the endometriosis group. Furthermore there was no significant difference in the size of the leading follicle between the endometriosis and the tubal infertility groups (Fig. 1). The mean size of the second leading follicle on day 0 in the clomiphene-only cycles (17.0, SEM 0.3 mm) was similar to that in the clomiphene plus FSH cycles (17.6, SEM 0.5 mm).

Table 1 shows the mean rate of growth of the leading follicle during the last 2 days before day 0. There was no significant difference between the three cycles monitored in the endometriosis group nor between the spontaneous cycles in the tubal infertility groups and any of the three cycles monitored in the endometriosis group.

Mean serum FSH levels on days -4 to 0 in spontaneous cycles did not differ significantly between the endometriosis and tubal infertility groups (Fig. 2). However, as might be expected in the clomiphene stimulated cycles, FSH levels were significantly higher on day -4 ($P < 0.05$) and significantly lower on day 0 ($P < 0.05$) compared with the spontaneous cycles. Furthermore, FSH levels were constantly higher in the clomiphene plus FSH stimulated cycles than in

Table 1. Rate of growth of the leading follicle as estimated by ultrasound during the last two days up to the reference point 0*

Cycles	n	Increase in follicular diameter (mm)	
		Day -2 to -1	Day -1 to 0
Tubal infertility group			
Spontaneous	12	1.4 (0.2)	2.1 (0.3)
Endometriosis group			
Spontaneous	17	1.7 (0.2)	1.9 (0.1)
Clomiphene stimulated	17	1.9 (0.1)	2.0 (0.1)
Clomiphene+FSH	17	2.1 (0.1)	2.2 (0.1)

Results are mean (SEM) values

* See text for explanation.

the spontaneous or clomiphene stimulated cycles on days -4 to 0 ($P < 0.001$)

Discussion

The dominant follicle during the mid and late

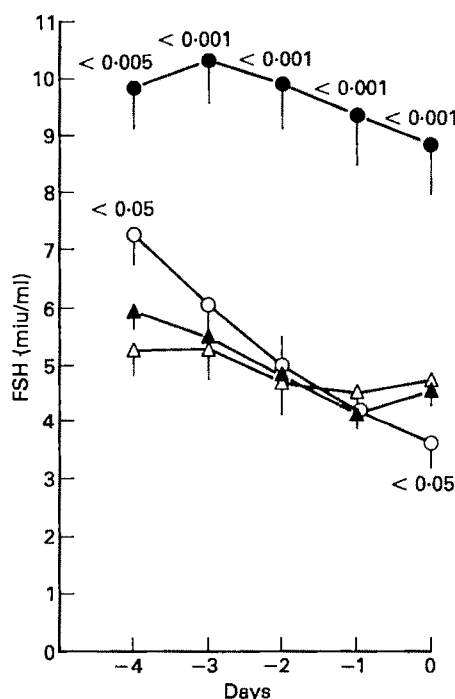


Fig. 2. Serum FSH levels (mean $\pm$ SEM) during the mid- to late follicular phase in 17 normally cycling women with minimal-mild endometriosis (spontaneous cycles Δ , clomiphene cycles $\circ$, clomiphene plus FSH cycles $\bullet$). Comparison with 12 spontaneous cycles in women with tubal infertility ($\blacktriangle$). Day 0 is the day on which the leading follicle reached or exceeded the size of 18 mm in diameter

follicular phase of spontaneous cycles showed a similar pattern of growth rate in women with endometriosis as in women with tubal infertility, the growth rate pattern was unchanged in clomiphene stimulated cycles. Although we did not treat the tubal infertility group with clomiphene, it has been reported that this compound stimulates faster follicle growth in such women (Lee-ventveld *et al.* 1985; Templeton *et al.* 1986). The present results are in contrast to those reported by Doody *et al.* (1988) who found that the rate of follicle growth during spontaneous cycles in women with endometriosis was slower than in normal women and was not corrected during clomiphene treatment. There are, however, methodological differences between the present and that study, which included women with all clinical stages of endometriosis, and in which the size of the follicle prior to ovulation in the endometriosis group was similar to that in normal women but the total period of follicle growth was longer. However, in that study the time of onset of follicle growth was taken as a reference point and this is not as easily defined as the day on which the follicle becomes 18 mm in diameter.

In the present study, the addition of exogenous FSH to clomiphene treatment did not alter the pattern of follicle growth in the endometriosis group. Similar data have not been published for women with endometriosis, but Templeton *et al.* (1986) noted that in women with tubal infertility clomiphene plus FSH stimulation resulted in follicles with larger diameters and with accelerated growth during the 2 days preceding the LH surge compared with spontaneous cycles. It should be emphasized, however, that up to 18 mm the follicle growth rate was similar to that in spontaneous cycles. Moreover, similar growth rates for the leading

follicle have been reported during treatment with clomiphene or FSH and in spontaneous cycles in women with unexplained infertility (Messinis & Templeton 1990). It is suggested, therefore, that women with minimal-mild endometriosis cannot be differentiated from other groups of infertile women on the basis of their folliculogenesis pattern either during spontaneous or stimulated cycles. Whether this means that the developmental potential of their oocytes *in vivo* is similar to that in the other infertile patients is not clear. So far a similar degree of ovarian response to stimulating agents and similar pregnancy rates have been observed in women with endometriosis (Jones 1986). The fact that the blood levels of FSH differed greatly between the spontaneous and the stimulated cycles suggests, in agreement with previous data (Messinis & Templeton 1990), that above a critical level FSH does not enhance follicle growth during the mid- and late-follicular phase of the cycle.

The present results also show that clomiphene plus FSH treatment can advance the pre-ovulatory stage of the dominant follicle in women with endometriosis. Since follicle growth rates were similar in stimulated and unstimulated cycles, this difference can be explained only by higher serum FSH levels during the early follicular phase of the stimulated cycles which results in an earlier recruitment of the dominant follicle, as has been suggested previously (Messinis & Templeton 1990).

Furthermore, in the present study, none of the stimulated women displayed an endogenous LH surge up to the time of hCG administration. This confirms previous data suggesting that clomiphene prevents the premature onset of the LH surge in superovulated cycles (Messinis & Templeton 1988). In that respect, women with minimal-mild endometriosis behave similarly to those with tubal or unexplained infertility.

In conclusion, we have demonstrated that development of the dominant follicle is not impaired in women with minimal-mild endometriosis. The pattern of follicle growth remains unchanged during superovulation induced by clomiphene, with or without FSH. It is suggested that the infertility in these women cannot be explained on the basis of the ultrasound characteristics of their follicles.

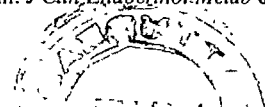
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Outcomes of referrals to gynaecology outpatient clinics for menstrual problems: an audit of general practice records

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Abstract

Objective—To determine referral rates and intermediate and long-term outcomes for patients consulting for menstrual disorders and referred by their general practitioner to gynaecology outpatient clinics

Design—General practitioners' records of referrals to outpatient clinics and retrospective audit of general practice notes to determine outcomes.

Setting—General practices in the Oxford Regional Health Authority area referring to 19 gynaecology outpatient clinics.

Subjects—205 patients aged 15–59, referred in 1983/4 and follow up in 1988/9.

Main outcome measures—Immediate outcomes: the initiation by hospital specialists of investigation, treatment or advice. Five year outcomes: general practice consultation rates and symptom prevalence.

Results—Of 18 754 index referrals recorded by 33 practices over a period of 6 months, 2513 (13%) went to gynaecology clinics. Menstrual disorders constituted 21% ($n = 539$) of the gynaecology referrals; there was more than three-fold variation between the practices in referral rates. In the 5 years following the index referral, of the 205 audited patients 167 (81%) had been admitted to hospital, 91 (44%) had had a hysterectomy (including 87 (60%) of the 145 patients referred for menorrhagia), 98 (48%) had dilatation and curettage; 25 (12%) received only drug therapy, and 10 (5%) had no active treatment for these symptoms from either the specialist or the general practitioner. Only 29 (14%) had consulted their general practitioners about menstrual problems in the 12 months preceding the audit.

Conclusions—Guidelines are needed to assist referral decision-making. If audit is to be used to promote good practice these guidelines should consider the patients' anxieties and preferences, as well as the most appropriate use of investigations and treatments.

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Recently there has been widespread interest in the potential of medical audit to assess the quality and appropriateness of clinical care. The interface between primary and secondary care is of interest to both hospital specialists and general practitioners. We report here the results of a general practice-based audit designed to describe the results of the treatment of women with menstrual problems referred to gynaecology outpatients departments.

Menstrual problems are commonly encountered in general practice and there is evidence

that women are increasingly likely to seek medical advice for these symptoms. General practitioners participating in the National Morbidity Survey recorded a rate of 30.7 consultations per 1000 female patients per annum for excess or irregular bleeding and a 73% increase in consultations for these conditions between 1971 and 1981 (RCGP 1986). A proportion of these patients are referred by their general practitioners to gynaecology outpatients departments, where they may be considered for surgical treatment.

Both general practice referral rates to gynaecology clinics and hysterectomy rates have been shown to vary widely, suggesting a lack of consensus about the appropriate rates of referral and surgical treatment for these conditions (Coulter & McPherson 1986, Coulter *et al.* 1988). There is some evidence that outpatient referral rates and elective inpatient admission rates are positively associated, suggesting that decisions made in general practice are an important determinant of hospital resource use (Coulter *et al.* 1990). There is a need for agreement between general practitioners and specialists on guidelines for appropriate referral of these patients.

General practitioners' reasons for referring patients to outpatient departments divide broadly into three groups: for investigation and diagnosis; for advice and reassurance; for treatment (Coulter *et al.* 1989). Any assessment of the appropriateness of referral needs to take account of these different objectives and to try to assess whether the referral was: (a) necessary for this particular patient (in the light of the presenting symptoms, age, previous treatment, etc.); (b) timely (neither too early nor too late in relation to the course of the disease); and (c) effective (the objectives of the referral were achieved).

At the time of our study there were no existing local guidelines against which referral decisions could be assessed. To aid the process of standard-setting we hoped to gather some descriptive data about the referral process and treatment outcomes by means of a follow-up study of patients who had been referred to gynaecology outpatients clinics.

Subjects and methods

In 1983/4 we co-ordinated a large-scale study of general practitioners' referrals to outpatients

clinics. The methods have been reported elsewhere (Coulter *et al.* 1989; Noone *et al.* 1989), but briefly the study involved 127 general practitioners in 33 practices in the Oxford Regional Health Authority area who kept records of all their outpatient referrals over a period of 6 months. (To avoid confusion the referrals recorded during this first phase of the study will be known as the index referral.) At the time of the index referral general practitioners completed a standard form that requested details of the patient's date of birth and sex; information about themselves and the specialty, hospital and district to which they were making the referral; and their diagnosis and the main reason for the referral.

Five years later, in 1988/9, we audited the general practice case notes of patients who had been referred for one of five 'tracer' conditions or symptom groups, one of which was menstrual disorders. The audit was conducted in 20 of the 33 practices and we examined the notes of each patient with this condition who was still registered with these practices and whose notes could be traced. Process measures included length of time from first consultation to referral, and waiting times for outpatient appointments. Intermediate outcomes (the immediate result of the referral) were the actions initiated by the specialists. The long-term outcome measure was general practice consultation rates for the index condition in the 12 months preceding the audit.

The audit was conducted by one of us (J.B.) using a portable computer. This recorded the data obtained from the general practice notes, including copies of referral letters and hospital discharge letters, in a standard format developed using the D-BASE III-Plus software package. The audit was carried out between October 1988 and June 1989. The data were then downloaded onto the university mainframe computer for analysis using the SPSS-X package. The data items collected are listed in Table 1. The results of the audit were discussed with general practitioners and specialists at a series of feedback seminars.

Results

Referral patterns

Of the 18 754 index referrals to outpatient departments, 2513 (13%) went to gynaecology clinics. (Referrals to clinics in obstetrics, paramedical specialties, and dentistry were excluded

Table 1. Data collected in audit of general practice records

Was this a first referral for these symptoms?
Length of time from first record of symptoms to first referral
Clinical, stress-related, work-related or other problems recorded at the time of referral
How long did patient have to wait for outpatient appointment?
Was this a private or an NHS referral?
Did patient attend the outpatient appointment?
Who saw the patient in the outpatient clinic?
Length of time in outpatient system
Re-referrals, cross-referrals, referrals to different specialists
GP's and specialist's diagnosis
GP's and specialist's tests and investigations
GP's and specialist's treatments (drugs, appliances, advice, hospital admissions)
Patient's consultations with GP in 12 months before referral
in 12 months after O/P appt
in 12 months prior to audit
Present symptom state

from the above total.) Referrals for menstrual disorders (ICD8 626.0-626.9) constituted 21% ($n = 539$) of the gynaecology referrals.

Annual age-specific referral rates were calculated for the 27 practices that were able to supply details of their list sizes broken down by age and sex. Figure 1 shows the distribution of referral rates for menstrual disorders for women in the 15-54 age-group. The rates for individual practices varied from a low of 0.82 per 1000 women to a high of 32.6 per 1000 ($\chi^2 = 66.0$, $df 26$, $P < 0.001$; coefficient of variation 62.5%). The mean annual rate was 10.2 per 1000 women in this age-group. There was three-fold variation in referral rates between the practices at the 80th and 20th centiles.

The following results refer only to those patients whose records were included in the follow-up study. General practitioners in the 20 practices involved in the follow-up study had referred 354 patients with menstrual disorders. We were able to trace the notes of 205 (58%) of these women. The remaining patients were no longer registered with these practices.

The patients

Most of the 205 patients whose notes were audi-

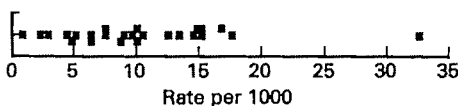


Fig. 1. Annual age-specific practice referral rates for disorders of menstruation (ICD 626): rates per 1000 women aged 15-54 in 27 practices

ted were in the age-group 30-49 ($n = 172$, 84%); three were aged less than 20; 13 were 20-29; and 17 were aged 50-59 at the time of the referral.

For 131 patients (64%) the index referral was the first time they had been referred for this condition, but 74 patients (36%) had been referred to an outpatients clinic on at least one previous occasion for a menstrual problem.

Table 2 shows the length of time between the first record of a general practice consultation for this condition and the index referral. Of those for whom this was the first referral, 31% were referred within a week and 43% were referred within a month of their first consultation for this condition. This group of patients included 18 who had intermenstrual bleeding, 9 who had fibroids, 7 who were anaemic and one with cancer of the cervix (according to the diagnoses recorded by the hospital specialists). The

Table 2. Length of time since first record of symptoms on general practice notes to date of referral letter

Time	First referral	Second or subsequent referral
	<i>n</i> (%)	<i>n</i> (%)
Under 1 week	40 (31)	- -
1 week to 1 month	16 (12)	- -
1 to 6 months	26 (20)	1 (1)
6 to 12 months	16 (12)	4 (5)
1 to 2 years	12 (9)	5 (7)
2 to 5 years	13 (10)	17 (23)
over 5 years	6 (5)	44 (59)
Patient record incomplete	2 (1)	3 (4)
Total	131 100	74 100

remaining 21 patients had menorrhagia or irregular periods only.

Many of the patients had consulted their general practitioners for other reasons in addition to menstrual problems during the 12 months before the index referral. Overall 42 (20%) of the women referred for menstrual disorders had consulted their general practitioners for other medical problems during this period and there were records of psycho-social problems in the notes of 56 (27%) of the patients.

The referral process

Most of the referrals were to gynaecologists' NHS clinics, but 25 patients (12%) were referred privately. A further 5 patients (2%) transferred from NHS to private care after their first outpatient appointment. Excluding the private referrals and those seen within a week of referral (which we have assumed were urgent referrals), the mean waiting time from the date on the referral letter to the date of the outpatient appointment was 41.2 days (95% CI 37.2–45.2). Two of the referred patients failed to attend the outpatients clinic for the index referral.

A total of 31 patients (15%) was discharged after one outpatient appointment, with no follow-up action on the part of the outpatients department, 18 of these had been referred for specialist advice, reassurance or diagnosis, but in nine the general practitioner had expected the specialist clinic to treat the patient. Seven of these 31 patients were subsequently re-referred by the general practitioner to the same specialist, and a further five were re-referred to a different specialist.

The remaining patients were kept under specialist care for a mean period of 216.3 days from the date of the referral to discharge (95% CI 190.2–242.4).

Investigation and treatment

Menorrhagia was the main presenting symptom for 145 (71%) of the patients. The remaining 60 women had a variety of conditions including symptoms of irregular or intermenstrual bleeding, or a diagnosis of pelvic inflammatory disease, or cervicitis. In the menorrhagia group 102 had associated problems, including pain, anaemia, prolapse, fibroids and endometriosis. Malignant neoplasms were diagnosed for two of the patients who presented with menorrhagia.

By the time of the follow-up audit, 98 of the referred patients (48%) had been admitted to hospital for dilatation and curettage; 91 (44%) had undergone hysterectomy; 25 (12%) had been prescribed a course of medication only; and 10 women (5%) had apparently received no active treatment for these symptoms other than advice and reassurance.

Table 3 shows the investigations and treatments offered to the patients referred for menorrhagia. Just over half had been prescribed drug treatment by their general practitioner before the referral. In the group of patients for whom one might have expected the general practitioner to prescribe drug treatment before referral—those presenting with menorrhagia but with no intermenstrual bleeding ($n = 129$)—the proportion who had in fact received drug treatment was 58% ($n = 75$). These patients received either hormonal preparations, particularly progestogens ($n = 51$) or danazol ($n = 8$), or non-hormonal drugs including inhibitors of prostaglandin synthesis ($n = 21$) or antifibrinolytics ($n = 5$). Some patients were prescribed more than one preparation before referral.

In all, 76% of the menorrhagia patients ($n = 155$) were admitted to hospital following the index referral and a further 12 were admitted following a re-referral, making a total of 81% admitted for in-patient investigation or treatment. Half of the patients referred for menorrhagia underwent curettage, including 44% of those in the under 35 age-group. The majority were admitted to hospital for dilatation and curettage, although six patients received aspiration curettage in the outpatients clinic. Just under half the patients ($n = 91$) eventually had a hysterectomy. Of these, the majority ($n = 87$) had presented with menorrhagia, so 60% of the 145 patients with this diagnosis had had a hysterectomy within the 5-year period.

Outcomes

Table 4 shows the mean general practice consultation rates in three periods: 12 months preceding the referral, 12 months following the first outpatient consultation, and 12 months preceding the audit in 1988/89. Mean consultation rates for menstrual problems decreased over the 5-year period (paired *t*-test, $t = 19.18$, $P < 0.001$), but these patients increased their rate of consultation for other problems during the

Table 3. Proportion of women in each age-group receiving different forms of investigation or treatment* (patients with menorrhagia only)

Treatment	Age-group of patients (years)							
	<35 (<i>n</i> = 32)		35–39 (<i>n</i> = 35)		≥40 (<i>n</i> = 78)		All ages (<i>n</i> = 145)	
	<i>n</i>	(%)	<i>n</i>	(%)	<i>n</i>	(%)	<i>n</i>	(%)
GP drug treatment before referral	21	(66)	18	(56)	41	(53)	80	(55)
Specialist-prescribed drug treatment	13	(41)	11	(31)	17	(22)	41	(28)
Curettage†								
(in-patient/out-patient)	14	(44)	19	(54)	40	(51)	73	(50)
Other procedures‡	4	(12)	1	(3)	5	(6)	10	(7)
Hysterectomy†								
(with or without other treatment)	18	(56)	18	(51)	51	(65)	87	(60)

*Some patients had more than one investigation or treatment.

†Following index referral or any subsequent referral.

‡IUCD removal or replacement, cervical biopsy, colposcopy, diathermy to cervix.

same period ($t = 3.19$, $P < 0.01$). Despite this apparent substitution, total mean consultation rates decreased over the 5-year period ($t = 3.93$, $P < 0.001$).

Only 29 (14%) of the women who had been referred to the outpatients clinic had consulted their general practitioners for menstrual problems in the 12 months preceding the audit. The remainder had not consulted for this reason during this period and for the purposes of the audit we have assumed that these patients' symptoms had resolved, either because of treatment or for some other reason.

Table 5 presents the outcomes according to the form of treatment received. Symptoms appear to have resolved for 78% of the 114 patients who did not undergo hysterectomy. Just over 20% of those who had received drug therapy or a procedure and 20% of those who had received no active treatment were still consulting their general practitioners about their menstrual problems. The four women who still had problems following hysterectomy included three who were consulting for symptoms related to the operation, including post-operative pain, and one woman who was receiving radiotherapy fol-

lowing a diagnosis of cancer of the endometrium.

Discussion

Our study has revealed considerable variation in referral rates for menstrual disorders, confirming the need to develop guidelines to assist referral decision-making. Guidelines should be based on an understanding of the management of these patients in both the general practice and the hospital and an audit of general practice records such as the one we have described can contribute to the process.

Any audit of general practice notes will be constrained by the quality, completeness and legibility of the records. Standards of record-keeping in the practices involved in our study were high, and the fact that the audit was undertaken by a health visitor with extensive experience of deciphering doctors' handwriting and medical terminology was a considerable advantage. Nevertheless, it was apparent that the notes were not always complete and this should be borne in mind when interpreting the results. It is also worth noting that it was only possible to

Table 4. General practice consultation rates before and after the index referral for 205 women

Study period	Menstrual problems		Other reasons		All consultations	
	Mean rate	(95% CI)	Mean rate	(95% CI)	Mean rate	(95% CI)
12 months						
Before referral	2.61	(2.38–2.84)	3.15	(2.58–3.72)	5.76	(5.14–6.38)
After outpatient appointment	2.10	(1.78–2.42)	3.01	(2.57–3.45)	5.11	(4.56–5.66)
Before audit	0.26	(0.16–0.36)	4.20	(3.66–4.74)	4.46	(3.90–5.02)

Table 5. Outcomes five years after index referral for menstrual disorders in 205 women

Treatment received	n (% of total)	Symptoms resolved	Symptoms persist
		n (%) ^a	n (%) ^a
No drugs, procedure or surgery	10 (5)	8 (80)	2 (20)
Drug therapy only	25 (12)	18 (72)	7 (28)
Procedure only†	27 (13)	23 (85)	4 (15)
Drugs and procedure only	52 (24)	40 (77)	12 (23)
Hysterectomy (with or without other treatment)	91 (44)	87 (96)	4 (4)
All patients	205 (100)	176 (86)	29 (14)

^a% of treatment group.

†Curettage, IUCD removal or replacement, cervical biopsy, colposcopy, diathermy to cervix

follow-up 58% of the patients referred 5 years previously. This is in accordance with estimates of 10% turnover per year in general practice lists, but is an additional limitation to this method of long-term follow-up.

Our findings do not support the view that women referred for menstrual disorders are abnormally high consulters (Stott 1983). Mean general practice consultation rates were close to the national average rate of five to six per annum among women in the age-group 16–64 (OPCS 1989). However, the rate of recording of psychosocial problems on the notes of these women was higher than that for some of the other tracer conditions examined in our associated studies. It is interesting that there was an inverse relation between consultation rates for menstrual problems and consultation rates for other problems. This suggests that referral is not a particularly effective means of reducing general practitioners' workloads, at least as far as this group of patients is concerned.

It is surprising that as many as 43% of these patients referred to outpatient clinics had first mentioned their symptoms to their general practitioners less than one month before the referral. Nearly half of these do not appear to have presented with symptoms which would have indicated immediate referral and yet their general practitioners do not appear to have tried a course of medication before referral.

This may be an indication that some general practitioners referred patients too readily, without first trying alternatives to hospital investigation and treatment. General practitioners who are under pressure from anxious patients, or who may be anxious themselves, may decide to refer at the first consultation. On the other hand, it may reflect general practitioners' perceptions of the length of waiting times for gynaecology

outpatient consultations and waiting lists for hysterectomy. Early referral may be seen as a way of reducing the time to admission, should this eventually become necessary. In the meantime the general practitioner can initiate a course of medication which may obviate the need for surgery.

There are many disadvantages to the drug treatments currently available and it is possible that patients' preferences for surgical treatment influenced the decision to refer. Many experts have stressed the importance that should be accorded to patients' preferences in treating menstrual problems (Noble 1985; Rees 1987, Dockeray *et al.* 1989). Unfortunately, general practice notes rarely include a record of patients' views of the available alternative treatments, so it is not possible to assess this reliably in an audit study.

The high proportion of women admitted to hospital after referral suggests that the hospital doctors concurred with the general practitioners' decisions. It also confirms the view that the decision to refer is tantamount to a decision that the patient requires some form of surgical procedure. The fact that 40% of the patients aged under 35 received dilatation and curettage is somewhat surprising, since it is unlikely to have a lasting therapeutic effect and its value as a diagnostic tool in women in this age-group is doubtful (Haynes *et al.* 1977; MacKenzie & Bibby 1978; Vessey *et al.* 1979). However, it is possible that practice has changed since our referral study was undertaken.

The new surgical alternatives to hysterectomy currently under development (Davis 1989; Magos *et al.* 1989) have received widespread publicity and this may result in an additional demand for treatment for menstrual disorders leading to an increased rate of referral. Com-

munity surveys indicate that the prevalence of perceived menstrual problems is much higher than the numbers of women who actually consult their general practitioners about them (Gath *et al.* 1987). The upward trend in general practice consultations seems likely to continue. On average general practitioners currently refer about one third of all patients consulting for menstrual problems but, as we have seen, there is wide variation in referral rates.

There is a high rate of surgical intervention following referral: at the time this study was undertaken dilatation and curettage was the most commonly performed operation in the Oxford Regional Health Authority and hysterectomy was eighth on the list (Oxford RHA 1986). It is therefore particularly important to assess all available therapies. In our study, symptoms had resolved for the majority of women in each of the treatment groups, including those who received no active therapy. Can we therefore assume that most of these women were referred and treated appropriately?

This is not an easy question to answer on the basis of the information we were able to collect. There were three limitations to our study (and, we suspect, to most medical audit studies using routinely-collected data): it included no information about case-severity; it included only those patients who were referred and excluded patients who were not referred for specialist care; and it excluded patients' subjective experiences of illness and outcomes and their treatment preferences.

In order to disentangle treatment effects from the natural history of the disease we would need a control group of patients with similar levels of symptomatology who were not treated. In order to make judgements about an appropriate rate of referral we would need data on patients' preferences and likely outcomes. Such information is often surprisingly unavailable in relation to many common forms of treatment.

We believe these basic points are worth emphasizing because of the current enthusiasm for audit. Medical audit is clearly a useful educational activity and scrutiny of general practice records in this way affords an excellent opportunity to look at the full course of an illness episode and its aftermath. However, the results of audit should be measured against standards based on carefully analysed research evidence. The necessary evidence on which practice guidelines should be based is often lacking.

The findings reported above and subsequent discussions with general practitioners and gynaecologists make us suggest that referral guidelines should be developed and, where necessary, research initiated to answer the following questions in relation to the three main reasons for referral.

(1) *Referral for investigation and diagnosis*

Is it appropriate to refer women under 40 years of age for dilatation and curettage? Should women with menorrhagia aged over 40 be referred for curettage before or after initiating a course of drug therapy? Should general practitioners be given the means to perform aspiration curettage as an alternative to referral? Should general practitioners make more extensive use of ultrasound investigations or menstrual blood loss measurement?

(2) *Referral for advice and reassurance*

Is it appropriate to use referral as a means of reassuring patients? If this is the main reason for referral, should it be made explicit in the referral letter?

(3) *Referral for treatment*

Which are the most effective drug treatments and for which patients are these not appropriate? Should non-hormonal preparations be used more widely? Which women should undergo hysterectomy in preference to other forms of treatment? At which stage in the course of an illness episode is it appropriate to recommend surgery? To what extent is it appropriate to allow treatment decisions to be guided by patients' preferences? Should patients be made more aware of the risks and benefits of the various treatment options?

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'Nuns, virgins, and spinsters'. Rigoni-Stern and cervical cancer revisited

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Summary. The view that nuns have a very low risk of cervical cancer is questioned. The historical evidence for this view is reviewed, from the beginning of the eighteenth century to the present. An estimate of the *actual* mortality rate from cervical cancer suggests that risk of death from this neoplasm among nuns is little different from that among the general female population. It is recommended that nuns should not be excluded from cervical cytology screening. When symptoms which might suggest cervical cancer arise in such women, full gynaecological assessment is necessary.

Present Department of Health policy regarding provision of cervical screening suggests that such screening is not necessary for 'nuns, virgins, and spinsters' (Warden 1990).

This policy is supported by the widely accepted view that cervical cancer is extremely rare among such women. Only if this view is correct is it reasonable to dispense with cervical screening in such women. If it were to be shown that such women had a lower, but still significant risk of cancer, then such an omission would be unreasonable.

Historical review

Rigoni-Stern

Answering a reader's question in the *British Medical Journal*, Drife (1984) states, regarding cervical cancer, that '... it is now well documented that the disease is rare in nuns and common in prostitutes ... a connection between intercourse and cervical cancer was apparently first suggested in 1842.'

Almost any paper on the epidemiology of cervical cancer mentions the work of Rigoni-Stern,

a surgeon in Padua in the mid-nineteenth century, who appears to have had an amateur interest in epidemiology.

At the 4th Congress of Italian Scientists, during a meeting of the surgical sub-section, Dr Gandolfi of Modena presented a paper on cirrhosis and cancer. Afterwards, a number of points concerning the epidemiology of cancer were made by Rigoni-Stern and although these were not included in the official report of the conference, Rigoni-Stern subsequently expanded his ideas and published these in a regional medical journal (Rigoni-Stern 1842).

Although his work is often quoted in the context of the epidemiology and aetiology of cervical cancer, it is important to remember that during his time the diagnosis of 'cancer of the womb' was not separated into carcinoma of cervix and corpus. Thus, it was impossible for Rigoni-Stern to make any comments on the incidence of deaths from *cervical* cancer. He did, in fact, find four deaths from cancer of the womb among 1288 deaths in nuns. Based on the numbers of deaths from cancer of the womb in the general population, six would have been expected (Skrabanek 1988). There is a suggestion of considerable under-reporting of this cancer, both in nuns and in the general population. The observations made are not of statistical significance.

In fact Rigoni-Stern was not so foolish as to

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draw any of the conclusions from these data that have been ascribed to him subsequently. He limited his observations on cancer of the womb to noting that the ratio of deaths from breast cancer to deaths from cancer of the womb was far greater in nuns (and single women) than in other women. This observation (of an excess of breast cancer in nuns) had already been made almost 150 years earlier by Ramazzini (1713). This would be expected on the basis of modern knowledge and is associated with the protective effect of pregnancy against breast cancer.

The quality of Rigoni-Stern's work is poor by modern standards. His paper is littered with errors of arithmetic. He adduces importance to differences which we would not now regard as being statistically significant. Interesting as Rigoni-Stern's observations were, it is somewhat surprising that his work is quoted as being authoritative. It is alarming that it is almost universally misquoted.

How such misquotation comes about is difficult to understand. Although the paper is written in Italian, there is no lack of clarity about his findings. Perhaps part of the explanation of this misquotation lies in the antiquity and obscurity of the journal in which the paper was published. It seems that once Rigoni-Stern's findings were misinterpreted many subsequent authors have merely accepted the accuracy of earlier 'quoters'. Two observations support this view—when the paper is quoted the title of the reference is often incomplete, the British Library, who do not hold a copy, have no record of any UK library holding a copy and had no record of having obtained a copy for any reader. (Recently his paper and the reference to it were published in full English translation, Rigoni-Stern 1987). It would be interesting to learn who first misquoted Rigoni-Stern and who was, therefore, responsible for the genesis of the myth. Skrabanek & McCormick (1989) have described this type of phenomenon as 'the Bellman's fallacy', whereby if an untruth is repeated often enough it becomes accepted as true.

Versluys

Versluys—a post-war Dutch epidemiologist—presented cancer-mortality statistics from the Netherlands for the years 1931 to 1935 (Versluys 1949). Among the general female population 4.91% of cancer deaths were due to carcinoma of the cervix. Deaths from cervical cancer were

more common in married women than unmarried (5.92% vs 2.33%). Versluys also calculated age-specific rates: these revealed, as expected, increasing rates in older women. The incidence of deaths from cervical cancer in single women in younger age groups (under 60 years of age) being about a quarter that in married women, and about half the incidence in older women.

Among 197 cancer deaths in nuns, Versluys found five deaths from cervical cancer—against an expected 4.6. These represented 2.5% of cancer deaths in nuns. His account is unclear but it appears that the 'expected mortality' from cervical cancer was based on an age-adjusted rate and that a correction may have been made for the nuns being older than the general population.

Versluys's study found cervical cancer to be no less common in nuns than in other single women. The incidence in single women being about half that in married women.

Gagnon

Fabien Gagnon was a French-Canadian gynaecologist who believed that pre-existing cervicitis was a major factor in the aetiology of cervical cancer. At the time of his work (Gagnon 1950) a number of authors were reporting the success of destructive treatment for cervicitis in preventing cervical cancer. These reports describe series of hundreds of women, mostly young, followed for relatively short periods of time. The incidence of death from cervical cancer at the time of these studies was of the order of one per 10 000 women per year. The incidence of death from cervical cancer among a small population of young women followed up for a few years would be expected to be less than unity. However, on this basis Gagnon and his contemporaries were able to convince themselves of the merit of their approach.

Gagnon was responsible for the provision of gynaecological care to a number of Roman Catholic convents. In order to test his hypothesis that cervicitis was an aetiological factor, he decided to study this population of nuns, whom he assumed would not have been at risk of cervicitis as they would not have been sexually active. Due to his position he was able to analyse the death records, going back many years, of a number of religious orders. He studied an 'annual average population of 13 000, covering a 20-year period'. He admitted that data were

inadequate in 3500 women, but found no deaths from cervical cancer in the remainder. Subsequently, he made a study of the records of various histology departments in the same catchment area. Not all histology departments in the catchment area were included. Cancers not biopsied would not have appeared in these statistics at all. Nevertheless histology department statistics revealed three cervical cancers in nuns and Gagnon assumed that these represented cases from the same population. Gagnon found 19 cases of cancer of the uterine corpus against three of the cervix. Unlike Versluys (1949) who compared the actual incidence to that expected, Gagnon used a ratio of cervical: uterine cancers. According to various sources he claimed that this ratio should be 6:1, whereas in his study the ratio appeared to be inverted. This ratio was obtained from the general population and so ignores the possibly increased risk of corpus cancer found in nulliparous women (such as nuns).

Gagnon's study revealed *at least* three cases of invasive cervical cancer among an 'annual average population' of nuns of 13 000 over a period of 20 years. This is an annual mortality rate from cervical cancer of 11.5/million nuns. At the time when Gagnon carried out his study, the mortality rate from cervical cancer among white women in North America was less than 100 per million women (Gardner & Lyon 1974). On the basis of Versluys' observations the rate among single white women would be expected to be about half of this. Kessler (1981) quotes rates among white women of 35 and 13 per 100 000 for ever-married and never-married respectively. Clearly the rate of cervical cancer mortality among nuns, found by Gagnon, did not differ significantly from that among other single women. The incidence among nuns was about one third that in ever-married women. Even Gagnon accepted that his estimate was likely to be artificially low due to the possible errors outlined above. This makes his conclusions seem even more dubious.

Logan

Logan was chief medical statistician at the General Register Office, in London—the predecessor of the Office of Population Censuses & Surveys (OPCS). He related marriage and child-bearing to cancers of the breast and uterus (Logan 1953). Overall cancer of the uterus (cer-

vix and corpus combined) was slightly less common in single women. Surprisingly cancer of the uterine corpus had a similar frequency in both groups, whereas cervical cancer was twice as common in married women. However, it is noteworthy that, of all cancers of the womb, 60% in single women and 45% in married women were of *unspecified* site. With regard to the numerically large group of 'unspecified' cancers, Logan felt that 'since they mainly represent an ill-defined mixture of cancer of two sites . . . it would serve no useful purpose to discuss them in detail.'

Towne

Janet Towne, a Chicago based gynaecologist, examined the rôle of child birth in cervical cancer (Towne 1955). She believed that 'If the rôle of pregnancies in carcinogenesis of the cervix is of etiological significance, then other variables connected with marriage or sexual congress must be partially associated as causative agents in the nonparous group of patients. If such a partial correlation exists, Gagnon's report of immunity of celibate women to cervical cancer would establish a relationship between this malignancy and a given factor'. In other words, as cervical cancer occurs in women who have had sex but no children, some other aetiological factor than childbirth must exist. If women who have never had sex did not get cervical cancer, then the occurrence of cancer in sexually active nulliparous women would probably be due to a sexual factor.

She conducted a retrospective analysis of known cases of cervical carcinoma over a 21-year period, from a radiotherapy unit. Of 574 cases, 16.3% were in nulliparous women, 6.4% occurred in unmarried women, 0.52% in members of religious orders. This represented three cases among nuns. Towne calculated a rate for cervical cancer in nuns of 1 in 1000. This would imply a rate of a third that in parous married women. However, this statistic is arrived at by rather dubious means. The denominator used was the number of nuns examined in the 21-year period (rather than the population from which they were derived). All cases were histologically squamous carcinomas.

In a further part of her study, she examined medical records from convents with an 'annual average population' of 10 000. The idea of comparing the incidence of such an 'annual average

population' with the rate in the general population, as was done by Gagnon, takes no account of the age and social class structures of the two differing population bases. An unspecified number of cases were disregarded 'because accurate pathologic information could not be obtained', but despite this she discovered three *further* definite cases. Although Towne's findings are often quoted as supporting those of Gagnon, she in fact stated 'Thus, the results would appear to be quite different from those of Gagnon, in that 6 nulliparous vaginal women were recorded with cervical carcinoma'.

She concluded that 'cervical malignancy can arise in women irrespective of virginity or parity'. She showed that the ratio of cancers of the cervix to those of the corpus was inverted in nulliparous and vaginal women. This observation clearly makes nonsense of any study—such as Gagnon's—which calculates a ratio, rather than an incidence rate, as was done by Versluys.

In her discussion she states 'to disseminate the idea that celibate or nulliparous women never develop cervical malignancies would be erroneous. Such misinformation creates the impression that it is unnecessary to suspect these women of, or examine them for, carcinoma of the cervix.' In the context of screening, this might be extended to imply that such misinformation should not be allowed to exclude such women from the cervical smear programme.

Stocks

Sir Percy Stocks, a senior research fellow of the British Empire Cancer Campaign, made use of the distinction that was made in national data from 1950 onwards of the specific site of 'cancers of the uterus'. He was thus able to study factors related to the incidence of cervical cancer, which had not previously been possible for England & Wales. In the years 1950 and 1951 there were 5287 deaths from cervical cancer (Stocks 1955).

Designating a value of 100 for 'all married women', comparative mortality ratios (this 'comparative mortality ratio' is identical to what is now described as *standardized* mortality ratio [SMR]) for all ages were 43 for single women, 84 for childless married women, 103 for married women with children and 125 for divorced or widowed women. Thus the rate for single women was half the rate for childless married

women, and just less than half the rate for parous women.

Fraumeni

Joseph Fraumeni and epidemiological colleagues at the US National Cancer Institute studied 31 658 white Catholic nuns in order 'to clarify the role of marital status in human carcinogenesis' (Fraumeni *et al* 1969).

Their study covered 41 religious communities for the years 1900 to 1954. They excluded all nuns who were not 'white, native-born, never-married'. Also excluded were nuns who 'had performed household or manual duties, were nurses or had served at foreign missions'. As a comparison group they used the total female population of Massachusetts (1900–1913) and the white female population of the US (1914–1954). The former group was used as the necessary data were unavailable for the whole US population until 1914. In fact, data on the incidence of specific gynaecological cancers were not available for these comparison groups. Estimates were obtained by the simple—but invalidated—method of assuming that the ratio of cancers at specific sites would be the same before 1930 as it was in 1930 to 1934, and calculating *estimated specific* rates for each genital site, based on the total for all genital cancers. The authors concede that this approach is not entirely accurate, it being known for instance that the proportion of uterine and cervical tumours varied considerably during this time. (In 1914 uterine tumours represented 91.6% of deaths from all genital cancers, and ovarian tumours 5.5%; in 1931 these values had changed to 83.0% and 13.1% respectively—clearly the proportions did not remain fixed during this time.)

As would have been expected, nuns suffered from an excess mortality from breast cancer. Except in the older age groups they had fewer deaths from malignancies of the genital tract.

Almost 11% of deaths from genital cancer among nuns were due to cervical tumours, compared to more than half in the comparison group. However, 'comparison is further obscured by the high proportion of uterine cancers of unspecified origin among nuns and, to a lesser degree, the general population'. At best this seems to indicate that the physicians responsible for diagnosis and death certification may not have pursued diagnosis as fully as in lay

women: at worst it may indicate a deliberate vagueness of diagnosis in many individual cases. As in many other studies, if only a proportion of 'unspecified site' diagnoses were more properly attributable to cervix, any difference between the two populations might disappear.

Fraumeni *et al.* (1961) concluded that 'The experience of nuns resembled that for all single women, who have a low rate for cancer of the cervix and high rates for cancers of corpus uteri and ovary.' They felt that this risk was probably hormonally mediated, reflecting the endocrine changes due to parity. Though also suggesting that 'an environmental factor related to coital experience appears responsible for the increased risk of cervical cancer among married women'.

Kinlen

Kinlen, an epidemiologist based at the Cancer Research Campaign unit in Oxford, examined the hypothesis that meat and fat consumption might be related to cancer mortality. He studied members of religious orders who had dietary regimens of differing strictness (Kinlen 1982). He failed to demonstrate a significant association between these dietary factors and cancer of the large bowel or breast.

He was much less concerned with cervical cancer. He did, however, note a lower incidence of cervical cancer among nuns than expected from the general population (2 cases seen as against 9.7 expected, $P < 0.01$). Deaths from cancer of the endometrium and of 'uterus site not specified' were grouped together and exceeded expectations for endometrium alone. It would seem that once again the low incidence of cervical tumours might, at least in part, be accounted for by an excess of unspecified site tumours.

What is the actual situation?

The mortality rate for cervical cancer in the United Kingdom is 74 deaths per million women per year (Cancer Research Campaign 1990). In England it is 76.8/million/year, 95.8/million/year in Wales (Office of Populations Censuses & Surveys 1989). It tends to be accepted that cervical cancer is a relatively common cause of death in women. In fact cervical cancer is only the seventh most common cause of death from malignant disease among women, and as such is of similar frequency to cancers of the bladder, oesophagus, uterine corpus and leukaemias (OPCS 1989).

Given the above facts, and accepting that the number of nuns is relatively small, one would not expect vast numbers of deaths from cervical cancer among women in religious orders.

In 1988 in England & Wales, there were 976 Anglican and 10 353 Roman Catholic nuns in religious communities (D. Skidmore, personal communication). Unfortunately no data are available concerning the age-distribution of this population. If the risk of cervical cancer among these women were assumed to be the same as among the general female population in the United Kingdom, then the expected mortalities from cervical cancer would be 0.84 deaths per year. During the years 1986–1988, inclusive, there were two deaths in female unmarried members of religious orders (*viz.*, nuns) (R. L. McGowan, OPCS, personal communication). This gives an observed annual rate of 0.66 deaths—not significantly different from that expected from the above calculation.

Discussion

None of the studies referred to has actually shown cervical cancer among nuns to be the rarity that has been claimed. Many of the studies are let down by unreliable historical data, often referring to a base population which is frequently not stable and may be unknown. It is impossible to calculate rates unless reliable values for both denominator and numerator are available. Most of the studies have discovered among nuns a disproportionate number of tumours of unspecified site. It is wrong to assume that all or even most of these tumours are non-cervical.

A number of studies have shown that marital status may be a risk factor for cervical cancer, in particular that the disease is more common in married, rather than single women. The use of such *relative risk factors* ignores the absolute risk. The majority of cervical cancers occur in married (or once married) women rather than single (never married) women, because most women have been married by the age of 55 years, the peak incidence for cervical cancer being from 55 onwards.

Malignancy of the uterine corpus is known to be associated with low parity. Nuns are thus more likely to develop such tumours. Calculations of the ratio of tumours of the uterine body to those of the cervix are therefore likely to be

increased even if the incidence of cervical cancer remains unchanged.

This review of previously published studies of the incidence of cervical cancer among nuns shows that the rate of death from this tumour in such women is comparable to that among other single women, and may not differ markedly from the rate in the general population.

Where cervical cancer occurs in a nun it is tempting to ascribe this to a less chaste past than her sisters, perhaps before entering a religious community. This attitude may reflect an unfair and erroneous assumption and, in any case, is of no practical value. We do not know whether cervical cancer arises in virginal nuns, although the work of Towne and others suggests that it can. As we cannot be expected to know the intimate past history of all nuns, none should be considered immune to cervical malignancy.

Careful review of the evidence reveals that there is no substantial objective evidence for the dogma that cervical cancer deaths are rare among nuns. Having convinced medical practitioners of this dogma three potential harms might result. Firstly being convinced that a cervical cancer could not arise in a nun—unless she had enjoyed a less than chaste past—a doctor seeing a nun might be tempted to dismiss this as a possible diagnosis and thus fail to give her the most appropriate treatment. Secondly, for similar reasons, when certifying the cause of death he might be led to record an incorrect diagnosis, either due to disbelief or to avoid a statement which might reflect on the deceased's character. In a number of studies of nuns the majority of deaths from 'cancer of the womb' were recorded as 'site not specified' and it is possible that accepting the dogma could introduce a bias which would appear to support the dogma. Thirdly as cervical cancer is regarded as a rarity in nuns, it is considered unnecessary to offer them cervical cytology screening (Warden 1990). We are doing a grave disservice to more than 10 000 women, if it is believed that such screening might be effective in preventing cervical cancer. Nuns should be offered routine cervical smears.

When a nun has symptoms suggestive of cervical cancer, that diagnosis should be considered as seriously as for any other woman. Irregular vaginal bleeding, intermenstrual bleeding or recurrent vaginal discharge, should lead to a full pelvic examination under anaesthesia.

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Increased plasma levels of vasoactive intestinal polypeptide in pre-eclampsia

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Abstract

Objective—To investigate the plasma vasoactive peptide (VIP) levels in pregnancies complicated by pre-eclampsia.

Design—A prospective clinical study.

Setting—University Department of Obstetrics, Tromsø, Norway.

Subjects—18 women with untreated gestational proteinuric hypertension between 32 and 40 weeks gestation (13 primigravid) and 8 women with normal pregnancies of similar gestational age.

Interventions—Fasting blood samples on two occasions, 10 min apart.

Main outcome measures—Plasma VIP measured by radioimmunoassay.

Results—Mean maternal plasma VIP was 13.9 (SEM 1.7) pmol/l in those with pre-eclampsia and 4.4 (SEM 0.5) pmol/l in normal pregnancies ($P < 0.0001$).

Conclusion—The increased levels of VIP in pre-eclampsia may represent a powerful compensatory mechanism to restore vascular perfusion of various organs, including the uterus and placenta.

Vasoactive intestinal polypeptide (VIP) is a regulatory peptide widely distributed in the human body (Said 1984). A relative abundance of VIP immunoreactivity, mainly representing VIP in nerve fibres, has also been demonstrated in the female genital tract (Larsson *et al.* 1977; Goodnough *et al.* 1979; Ottesen 1983). VIP was originally discovered because of its potent vasodilatory and muscle-relaxing effects (Said & Mutt 1970). Subsequently, it has been shown that VIP exerts similar effects in the female genital tract (Ottesen *et al.* 1982, Ottesen 1983;

Hansen *et al.* 1988). We have reported previously that plasma VIP levels become significantly elevated at delivery and in the immediate post partum period (Holst *et al.* 1986), whereas levels remain essentially unchanged throughout normal gestation (Ottesen *et al.* 1982, unpublished results). We have suggested that VIP may play a beneficial role during delivery because of its effects on smooth muscle activity (Holst *et al.* 1986). Since it has been demonstrated that VIP has both central and systemic vasodilating properties, it has been postulated that this substance may be involved in the control of blood pressure (Said 1983). Indeed, this seems to be the case in spontaneously hypertensive rats (Chatelain *et al.* 1980; Avidor *et al.* 1989). Moreover, as a consequence of the generalized vasodilating properties of VIP, this substance induces systemic hypotension (Said 1983). Similarly, VIP may play a role in pre-eclampsia, since increased vascular resistance and decreased circulating volume with impaired perfusion of various organs are recognized as important pathophysiological features of this disease. The aim of the present study was there-

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fore to determine plasma VIP concentrations in pre-eclamptic patients, compared with a control group of normotensive pregnant women.

Subjects and methods

The study group consisted of 18 patients, 13 of them primigravidae, mean age 26 years (range 17–41 years) with untreated pre-eclampsia during singleton pregnancies. Pre-eclampsia (gestational proteinuric hypertension) was defined according to the new classification of Davey & MacGillivray (1988), i.e., diastolic blood pressure of ≥ 90 mmHg on two or more consecutive occasions at least 4-h apart, and proteinuria of ≥ 300 mg/24 h. All women returned normotensive without proteinuria within 6 weeks postpartum. The gestational length at the time of blood sampling varied between 32 and 40 weeks.

Eight normotensive and healthy pregnant women without proteinuria, six of them primigravidae, mean age 31 years (range 24–38 years) served as a control group. Data from this group have been published before (Holst *et al.* 1989).

Since plasma VIP levels remained unchanged during normal pregnancy (unpublished results), pooled data from weeks 32 to 40 (24 observations) were used for comparison in the present study.

All patients participated in the study after first giving their informed consent. None of the women had a history of hypertension or chronic renal or gastrointestinal disease. None had taken any drugs, apart from iron and folic acid supplements, for at least 3 months before pregnancy.

Fasting blood samples were obtained as described previously (Holst *et al.* 1986). On each occasion, two blood samples were drawn with a 10-min interval. Plasma VIP was determined as the mean of the VIP immunoreactivity in these two samples.

Table 1. Blood pressure, proteinuria and plasma vasoactive intestinal polypeptide (VIP) levels in 18 pre-eclamptic patients and eight controls

	Pre-eclampsia	Control
Blood pressure (mmHg)		
Systolic	154 (2)	112 (1)
Diastolic	98 (1)	74 (1)
Proteinuria (mg/24 h)	2100 (300)	0
Plasma VIP (pmol/l)	13.9 (1.7)	4.4 (0.5)

Plasma VIP was measured by a radioimmunoassay method described previously (Burhol *et al.* 1978).

Statistical analyses

Statistical analyses used Student's *t*-test. $P < 0.05$ was considered statistically significant. The results are presented as means (SEM) values.

Results

The results are summarized in Table 1. In the pre-eclamptic patients, the mean systolic blood pressure was 154 (SEM 2) mmHg and the mean diastolic was 98 (SEM 1) mmHg. The urinary protein excretion averaged 2100 (SEM 300) mg/24 h. Four of the patients had severe pre-eclampsia, here defined as blood pressure $\geq 160/100$ mmHg and proteinuria ≥ 3000 mg/24 h. The remaining 14 patients were classified as having mild pre-eclampsia. There were four patients who gave birth to babies whose birthweight was below the 2.5th centile.

Plasma VIP concentrations were substantially higher in the pre-eclamptic patients (mean 13.9, SEM 1.7 pmol/l) than in the normotensive pregnant women of comparable gestational length (4.4, SEM 0.5 pmol/l). This difference was highly significant ($P < 0.0001$) (Fig. 1).

Patients with severe pre-eclampsia had non-significantly lower plasma VIP levels (12.1, SEM 3.0 pmol/l) than those with mild pre-eclampsia (14.4, SEM 2.0 pmol/l, $P = 0.59$). Pre-eclamptic patients giving birth to small-for-gestational age babies had slightly but non-significantly higher plasma VIP concentrations (16.8, SEM 3.6 pmol/l) than women with normal

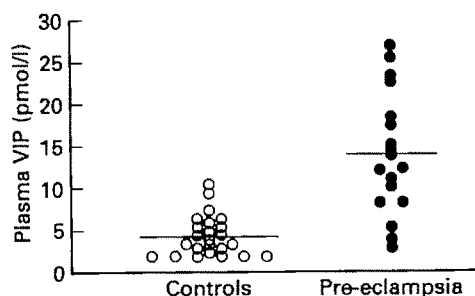


Fig. 1. Individual plasma vasoactive intestinal polypeptide (VIP) levels (pmol/l) in controls and pre-eclamptic patients. The horizontal bars represent mean values.

weight offspring (12.5, SEM 2.2 pmol/l, $P = 0.35$).

Discussion

This study shows for the first time that plasma VIP concentrations are substantially increased in pre-eclampsia, but no significant differences were found between mild and severe pre-eclampsia, nor between pre-eclamptic patients giving birth to small and normal weight babies. However, the number of observations in these subgroups are too small to draw definite conclusions.

Since plasma levels of the vasodilating agent VIP were markedly increased in pre-eclamptic patients and this condition is characterized by vasoconstriction, altered VIP concentrations cannot be a causative factor in pre-eclampsia. Rather, VIP could be a powerful compensatory mechanism to restore vascular perfusion to different organs, including the uteroplacental unit. Indeed, it has been shown that VIP induced an increase in myometrial and total uterine blood flow in non-pregnant women (Ottesen 1983), and a relaxation of the uteroplacental arteries in specimens from pregnant women at term (Hansen *et al.* 1988). Moreover, pregnancy in rats was associated with significant rises of immunoreactive VIP concentrations in the spinal cord (Chery-Croze *et al.* 1986), which contains efferent neurones innervating the pelvic organs. Most recently it has been reported that VIP significantly increased the production of prostacyclin, while it slightly reduced that of thromboxane in perfused umbilical arteries from pre-eclamptic pregnancies (Haugen *et al.* 1990). These findings seem to be of special interest together with our observation, since an imbalance between vasodilator (i.e., prostacyclin) and vasoconstrictor (i.e., thromboxane) eicosanoids has indeed been found in pre-eclampsia (Remuzzi *et al.* 1980). Our view is further supported by the finding of increased VIP mRNA content in the brain of spontaneously hypertensive rats (Avidor *et al.* 1989). Finally, platelet aggregation is inhibited by VIP (Ercal *et al.* 1988), thus providing an additional compensatory mechanism to restore uteroplacental blood flow.

The general smooth muscle-relaxing effects of VIP also applies to the myometrium. Thus, VIP has been found to inhibit myometrial contractions in tissues from non-pregnant women (Otte-

sen *et al.* 1982). By contrast, VIP had no effect on the myometrium of pregnant subjects (Ottesen *et al.* 1982). Because of this observation and since VIP serves as a putative oxytocin-releasing agent (Ottesen *et al.* 1984), the clinical observation that pre-eclamptic patients are in a state of relative myometrial hypercontractility may be mediated by oxytocin caused by the increased plasma VIP levels.

Most investigators have found increased circulating prolactin (PRL) levels in pre-eclampsia (Hayashi *et al.* 1982, Davison 1989). Since VIP has been shown to stimulate PRL release both in vivo and in vitro (Ottesen *et al.* 1981; Said & Porter 1979), this substance may be operative in causing the elevated PRL levels observed in pre-eclamptic patients.

Specific receptors for VIP have been demonstrated on lymphoid cells, and VIP, among other neuropeptides, has been shown to modulate a variety of lymphocyte functions, and hence immune response (Ottaway 1988). Therefore, increased VIP-release in pre-eclampsia could play a regulatory role for the immunological changes in this disorder (Davison 1989).

Unfortunately, having demonstrated that plasma VIP concentrations are substantially elevated in pre-eclampsia, we cannot say at what stage in pregnancy this increase occurs. However, women who are destined to develop pre-eclampsia have an increased vascular sensitivity to endogenous pressor substances many weeks before hypertension becomes manifest (Gant *et al.* 1973). Because of the postulated compensatory role of VIP in this disease, we may therefore suggest that the increased plasma VIP levels represent an early event in the course of pre-eclampsia. If so, measurements of plasma VIP levels could represent a valuable tool in the pre-clinical diagnosis of pre-eclampsia. It may also be speculated whether VIP or its analogues can be used in the treatment of this disorder.

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Reproducibility of ultrasonic measurement of fetal cardiac haemodynamics

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Summary. Two observers made independent estimates of volume flow across all four heart valves in 27 fetuses using a combination of cross-sectional and Doppler echocardiography. There were considerable discrepancies between observers in volume flow estimation arising from inconsistency both in cross-sectional and in Doppler measurements. One observer also produced a second estimate by making new measurements from the original recordings. There was considerable within-observer variability which was mainly due to errors in cross-sectional measurements. The problems of applying this technique to fetal cardiac haemodynamics are discussed.

Combined cross-sectional and Doppler echocardiography is widely used to characterize cardiac haemodynamics in children (Alverson *et al.*, 1982) and adults (Huntsman *et al.* 1983). Maulik *et al.* (1984) first described the use of ultrasonic techniques for measuring fetal cardiac haemodynamics with reference to the pulmonary valve. There followed reports of volume flow measurement by ultrasound at all the fetal heart valves (Kenny *et al.* 1986; Reed *et al.* 1986; Allan *et al.* 1987; De Smedt *et al.* 1987). It has been further suggested that the technique may be capable of diagnosing pathologically increased or decreased volume flow in individual fetuses (Maulik *et al.* 1985; Reed *et al.* 1987; Yagel *et al.* 1988).

Invasive methods cannot be used in the human fetus, and the accuracy of ultrasonic

measurement of cardiac blood flow in the fetal heart has not been validated. There have been no reports of studies comparing invasive and non-invasive methods in animal fetal hearts. There have been a number of reports concerning aspects of the reproducibility of the components used to calculate volume flow, namely, cross-sectional measurements (Kenny *et al.* 1986; Cartier *et al.* 1987, Al Ghazali *et al.* 1989) and Doppler velocities (Kenny *et al.* 1986; Al Ghazali *et al.* 1989). The reproducibility of ultrasonic measurement of volume flow through the fetal heart has not been studied directly. The aim of our present study was to examine the reproducibility of ultrasonic estimates of volume flow in the human fetal heart and to assess the potential of the method for detecting abnormal flows

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Subjects and methods

Background

In order to measure the volume of blood passing across a valve during the cardiac cycle two measurements are required: the cross-sectional area of the valve and the length of the column of blood passing through the valve. Multiplication of the volume flow for each cycle by the heart rate gives the volume flow per unit time

Cross-sectional ultrasound is used to calculate the area of the valve. The valve area can be

measured directly by planimetry but in the fetus all investigators assume heart valves to be circular in cross-section and measure a single diameter only. The length of the column of blood passing through a valve can be estimated by the Doppler principle. When a beam of ultrasound is transmitted towards a moving object (in this case the column of blood) there is backscatter of ultrasound at a different frequency. The change in frequency (Df) can be related to the velocity (v) of the moving object by the formula:-

$$v = \frac{Df \times c}{2f_e \times \cos\theta}$$

c = average speed of propagation of sound in tissue

f_e = emitted frequency of ultrasound

θ = theta, the angle between the ultrasound beam and the direction of travel of the object.

All blood passing through a valve does not travel at a constant velocity and thus a profile of velocities is obtained for each beat. This can be displayed as a waveform by fast Fourier analysis and its integral represents the length of the column of blood. The value of θ can be estimated from cross-sectional echocardiography. When the angle is less than 30° , the cosine of θ is close to 1 and this value can therefore be used in the calculations.

Methods

Twenty-seven pregnant women were recruited from the antenatal clinic. All procedures were explained and each woman gave informed consent. Approval was given by the ethics committee of Newcastle Health Authority.

All women were healthy and length of gestation was confirmed by a routine ultrasound scan at 18 weeks gestation. All pregnancies were uneventful and resulted in the birth of healthy infants at term. The women were recruited into three equal groups (A, B and C) according to gestational age. Table 1 shows the characteristics of the groups.

Each woman was scanned independently by two observers. One observer (A.H.) was a physiological measurement technician with extensive experience in adult, paediatric and fetal echocardiography. The other observer (A.B.) was medically qualified and had received 5 months training in fetal echocardiography before the start of the study.

The women were examined using an Advanced Technology Laboratories Ultramark 4 ultrasound system. For cross-sectional imaging a 5 MHz linear array probe (axial resolution 0.6 mm, lateral resolution 1.0 mm) was used where possible. In some fetuses of advanced gestation this probe gave inadequate depth of field and an Access C 3 MHz mechanical sector probe (axial resolution 1.5 mm, lateral resolution 1.8 mm) was used. Pulsed Doppler recordings were made using the Access C probe in all cases. At all times the system was used on the lowest power setting that would provide adequate signal quality. At full power the manufacturers specify power outputs of 26.5 mW (Access C in 2D imaging), 41.3 mW (Access C in pulsed Doppler mode) and 29.0 mW (Linear array: 5.0 MHz). Specifications for the spatial peak value of the temporal average intensity (I_{spta}), also with power set at maximum, are 27.0 mW/cm² (Access C in 2D mode), 874 mW/cm² (Access C in pulsed Doppler mode) and 6.2 mW/cm² (Linear array 5.0 MHz).

The women were examined in a semi-reclining position with a small degree of left lateral tilt. Each observer was limited to 15 min of scanning to minimize fetal ultrasound exposure.

The cross-sectional images were recorded on video tape. Where possible, sufficient footage was recorded to allow the measurement of each valve diameter from five cycles. The tapes were later played back through a Hewlett-Packard 77500B ultrasound system. Measurements were made using the on-screen caliper system and frame advance facility. Measurements were calibrated from the centimetre scale displayed with the ultrasound image. The atrio-ventricular

Table 1. Characteristics of the women recruited to the study

Group	<i>n</i>	Range of gestation (weeks)	Age (years)		Birthweight (g)	
			Mean	Range	Mean	(SD)
A	9	13-21	29.0	25-33	3776	(424)
B	9	22-31	30.1	25-35	3204	(326)
C	9	32-40	26.1	22-31	3646	(450)

Table 2. The causes of failure to obtain recordings

	Observer		Total
	A B.	A H	
Diameter measurement			
Fetal position preventing adequate views of valve	19	5	24
Inadequate image quality	8	6	14
Fetal activity or breathing	4	0	4
Total	31	11	42
Velocity integral			
Fetal position preventing alignment of sample volume with $\theta < 30^\circ$	17	13	30
Fetal activity or breathing	8	1	9
Damaged recording	1	0	1
Total	26	14	40

Note there are 108 possible measurements of diameter or flow integral per observer (four valves in each of 27 subjects)

valves were imaged from a four-chamber view (Allan *et al.* 1980). Measurements were made at the level of the valve anulus from inner wall to inner wall, immediately after valve opening. The outlet valves were imaged with the roots of the aorta or pulmonary artery viewed in the long axis. Diameters were measured from inner wall to inner wall at the level of the valve insertion immediately after valve opening.

The pulsed Doppler sample volume of 1.5 mm

in length was placed immediately distal to the valve, assuming flow to be at right angles to the orifice. If possible, the Doppler beam was placed in a direction parallel to the presumed direction of flow ($\theta = 0^\circ$). If this was not possible, the sample volume was rotated to the direction of flow and an estimate of θ was obtained. The velocity waveforms were recorded on to thermal video copy paper. At each valve an attempt was made to obtain five consecutive waveforms. The

Table 3. Volume flow estimations by the two observers and previously reported values

		Estimated volume flow (ml/min)								
Gestational age group		Observer A B			Observer A H.			Kenny (1986)	De Smedt (1987)	Allan (1987)
(weeks)	Valve	<i>n</i>	Mean	(SD)	<i>n</i>	Mean	(SD)	Mean	Mean	Mean
A (19–21)	Aortic	2	30	(7)	7	58	(16)	118		70
	Pulmonary	6	59	(11)	5	97	(25)	132.		93
	Tricuspid	7	112	(41)	8	143	(54)		105	140
	Mitral	6	80	(22)	5	123	(39)		84	109
B (29–31)	Aortic	7	177	(75)	8	215	(93)	282		269
	Pulmonary	6	237	(51)	4	308	(69)	302		361
	Tricuspid	9	620	(328)	9	552	(204)		372	428
	Mitral	9	564	(223)	9	378	(141)		333	333
C (38–40)	Aortic	2	306	(181)	5	393	(206)	676		647
	Pulmonary	3	400	(247)	8	733	(333)	692		866
	Tricuspid	4	813	(517)	8	1104	(342)		915	883
	Mitral	5	808	(521)	7	596	(161)		820	686

Kenny *et al.* (1986): $n = 72$, pulmonary valve; $n = 75$, aortic valve

De Smedt *et al.* (1987): $n = 28$ for both valves, patients were studied every 4 weeks from 15–20 weeks.

Allan *et al.* (1987): total number of patients studied = 120. Volume flow was measured at all valves in 36 patients, in the remaining 84 data were obtained from 2 or 3 sites

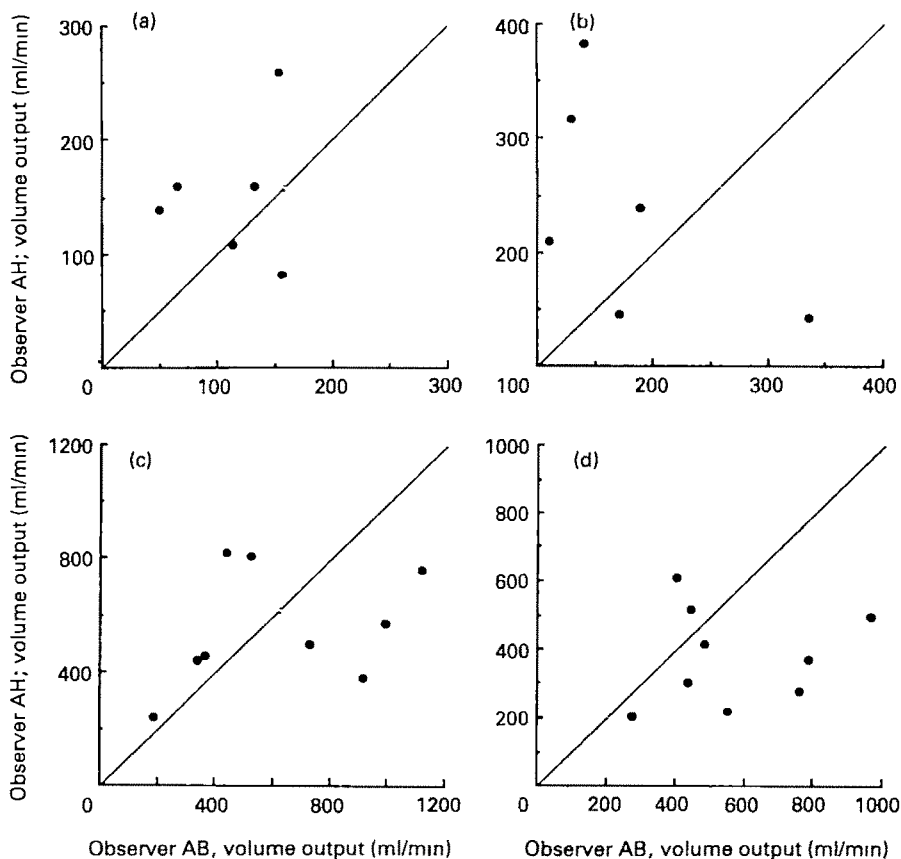


Fig. 1. Plots comparing the estimates by two observers (A.B. and A.H.) of volume flow at: (a) Tricuspid valve in group A patients; (b) Aortic valve in group B patients; (c) Tricuspid valve in group B patients; (d) Mitral valve in group B patients. These refer to cases (summarized in Table 4) where there were five or more pairs of observations.

waveforms were not accepted unless θ was $\leq 30^\circ$. Velocity integrals were derived by means of a graphics tablet linked to an Apple II microcomputer. Heart rate was measured from the Doppler recordings. Measurements were calibrated from the scales displayed with the Doppler image.

Volume output (ml/min) was calculated from the mean values of diameter (D , cm), velocity integral (VI , cm) and heart rate (HR , min^{-1}) according to the following formula:

$$\text{Volume output} = \frac{\pi \times D^2 \times VI \times HR}{4}$$

Both observers measured their recordings independently and one observer (A.B.) made a second measurement of his recordings between 2 and 3 months later.

Results

Feasibility of measurement

Recordings adequate for measurement of flow could not always be obtained in the time allotted. Table 2 lists the reasons contributing to the failure of measurement. An unfavourable fetal position was the commonest problem.

Of the 108 possible estimates of volume flow (four valves in each of 27 subjects) observer A. B. obtained 66 (61%) while observer A.H. obtained 84 (78%). Success rates varied in the different gestational groups. In group A fetuses (19–21 weeks) observer A.B. obtained 58% and observer A.H. 69%, in group B fetuses (29–31 weeks) both observers obtained 68% and in group C fetuses (38–40 weeks) observer A.B. obtained 39% while observer A.H. obtained 78%. Both observers found measurements

Table 4. Between-observer comparison of volume flow estimations

		Estimated volume flow (ml/min)			
Group	Valve	n	Mean	SD	SD of difference
A	Tricuspid	6	131	(40)	70
B	Aortic	6	211	(39)	157
B	Tricuspid	9	586	(219)	326
B	Mitral	9	471	(139)	248

Note this table includes only cases where there were five or more pairs of observations.

easier to obtain at the atrio-ventricular valves than at the arterial valves.

Between-observer comparison

Table 3 shows the mean values in the three gestational groups. The values from each observer are shown along with mean values derived from previously published work. Both observers reported similar mean values which were compatible with previous work. However, both observers reported consistently greater values of volume flow through the atrio-ventricular valves than through the corresponding arterial valves.

Mean values of each observer were similar but there were considerable differences between values obtained from individual fetuses. In Fig. 1, the pairs of observations are compared where more than five pairs of values were obtained. Table 4 shows a comparison of the mean (SD) values of these cases with the standard deviation of the difference between the pairs of observations. In 5% of cases the between observer difference would be expected

to be greater than 2SD of observed difference. The variation between the observers is greater than the variation between individual fetuses.

Table 5 shows the same comparison for the measurements of diameter, velocity integral and heart rate. Poor reproducibility of these measurements contributed to the low reproducibility of volume flow.

Within-observer comparison

Table 6 shows the results of the measurements of volume output made on two occasions by observer A.B. and Table 7 demonstrates the results of diameter, velocity integral and heart rate. Velocity integral and heart rate measurement were reasonably consistent but there was low reproducibility of diameter and volume flow measurement.

Discussion

It is difficult with this technique to obtain good flow data from every fetus, its clinical usefulness is therefore limited. The problem is usually an unfavourable fetal position. The success rate might be improved by allowing more time for the scan or repeating it on the following day. The success rate should also improve with experience. It is noteworthy in our study that the less experienced observer failed more often to obtain adequate recordings although our success rates are similar to those previously reported (Maulik *et al.* 1984; Reed *et al.* 1986; Kenny *et al.* 1986).

In adults, the reproducibility of ultrasonic measurement of volume flow appears to be adequate for clinical purposes. Ihlen *et al.* (1987)

Table 5. Between-observer comparison of diameter, velocity integral and heart rate measurements

		Diameter (cm)			Velocity integral (cm)			Heart rate (beats/min)					
Group	Valve	n	Mean (SD)		SD of difference	n	Mean (SD)		SD of difference	n	Mean (SD)		SD of difference
A	Pulmonary	7	0.31	(0.02)	0.06								
A	Tricuspid	7	0.52	(0.04)	0.07	8	4.3	(1.0)	1.4	8	146	(6.0)	4.6
A	Mitral	6	0.50	(0.01)	0.10	8	3.7	(0.9)	0.9	8	143	(4.5)	3.1
B	Aortic	7	0.46	(0.05)	0.11	7	8.3	(1.4)	1.8	7	139	(15.0)	9.3
B	Pulmonary	8	0.51	(0.07)	0.09								
B	Tricuspid	9	0.92	(0.13)	0.20	9	6.2	(1.3)	1.4	9	136	(8.5)	10.6
B	Mitral	9	0.84	(0.08)	0.15	9	6.0	(1.4)	1.3	8	139	(9.7)	5.5
C	Tricuspid					6	6.5	(1.1)	1.1	6	134	(8.0)	8.4
C	Mitral					7	5.7	(1.3)	1.3	7	134	(6.6)	12.6

Note this table includes only cases where there were more than five pairs of observations

Table 6. Within-observer comparison of volume flow estimations

Group	Valve	n	Estimated volume flow (ml/min)		
			Mean	SD (SD)	SD of difference
A	Pulmonary	6	67	(11)	9
A	Tricuspid	7	124	(41)	14
A	Mitral	6	95	(20)	14
B	Aortic	7	167	(56)	28
B	Pulmonary	6	239	(45)	22
B	Tricuspid	9	590	(239)	231
B	Mitral	9	528	(153)	94
C	Mitral	5	861	(441)	111

Note this table includes only cases where there were five or more pairs of observations

concluded that no systematic errors were introduced by different observers and Robson *et al* (1987) described acceptable within-observer reproducibility.

In children and fetuses there is limited information about the reproducibility of volume flow estimation. However, several investigators have considered the reproducibility of some of the components required for its calculation (Hans  us *et al.* 1988; Claflin *et al.* 1988; Veille *et al.* 1989; Reed *et al.* 1986; Kenny *et al.* 1986; Allan *et al.* 1987; Cartier *et al.* 1987; Al Ghazali *et al.* 1989). Mostly these investigators have used inappropriate statistical methods, such as correlation, to assess the agreement between repeated measurements (Blard & Altman (1986)). It is thus difficult to draw conclusions from their work and this shows the need for

greater understanding and more consistency in the reporting of reproducibility investigations.

In our experience the reproducibility of the estimation of volume flow within the fetal heart is poor. There was a large variation between observers resulting from poor reproducibility of both diameter and velocity integral.

Diameter measurement is particularly important since the value is squared in volume flow calculations. Although biological variation in the diameters of fetal heart valves may be important, it appears from our study that observer error is the main problem. Fetal heart valve diameters range from about 0.2 cm to 1.5 cm. For smaller diameters these values are close to the limits of resolution of our equipment. Thus vessel walls are indistinct and there can be considerable subjectivity when placing the measurement calipers. Improvement of resolution will improve the potential precision of measurement. A further problem may be the difficulty in reproducing exactly the same cross-sections for measurement of different examinations. Small changes in the angulation of the scanner head will slightly change the cross-section and affect the valve measurement.

The low reproducibility of velocity integral measurements between observers has not been reported previously. This may result from short-term changes in fetal heart function. Arduini (1987) found that Doppler mean peak velocities of blood flowing through the fetal aorta and pulmonary valve were significantly increased during fetal activity. There may also be methodological problems. Fetal Doppler velocity waveforms are small and the display is close to maximum mag-

Table 7. Within-observer comparison of diameter, velocity integral and heart rate measurements

Group	Valve	n	Diameter (cm)			n	Velocity integral (cm)			n	Heart rate (beats/min)		
			Mean	SD (SD)	SD of difference		Mean	SD (SD)	SD of difference		Mean	SD (SD)	SD of difference
A	Aortic	6	0.29	(0.04)	0.03	6	5.5	(0.9)	0.2	6	144	(6.8)	0.6
A	Pulmonary	7	0.29	(0.04)	0.03	6	6.8	(1.6)	0.3	6	146	(2.2)	0.6
A	Tricuspid	8	0.50	(0.03)	0.06	8	4.3	(1.2)	0.1	8	146	(4.0)	0.6
A	Mitral	6	0.50	(0.05)	0.06	9	3.3	(0.8)	0.1	9	144	(4.6)	0.7
B	Aortic	7	0.43	(0.06)	0.07	8	8.3	(1.6)	0.4	8	141	(12.3)	0.5
B	Pulmonary	8	0.46	(0.08)	0.04	6	9.8	(2.3)	0.4	6	137	(4.8)	1.4
B	Tricuspid	9	0.92	(0.12)	0.17	9	6.2	(1.4)	0.6	9	139	(11.4)	1.2
B	Mitral	9	0.88	(0.10)	0.14	9	6.3	(1.4)	0.2	9	137	(10.2)	0.7
C	Pulmonary	6	0.63	(0.13)	0.05	—	—	—	—	—	—	—	—
C	Tricuspid	5	1.24	(0.19)	0.21	7	6.4	(1.2)	0.5	7	132	(9.8)	1.0
C	Mitral	6	1.10	(0.15)	0.22	7	6.0	(1.8)	0.3	7	135	(11.4)	0.9

Note this table includes only cases where there were more than five pairs of observations

nification. This can lead to an indistinct image for measurement. Further errors may be related to sampling. The angle θ can only be estimated in two dimensions. Slight changes in the scan plane may affect the appreciation of the angle and render velocity measurements inaccurate. Alternatively small movements of the probe or slight fetal movement may lead to inaccurate sampling. The formula used to calculate volume output is based on the assumption that flow through the fetal heart valves is laminar with a flat profile. This is probably a reasonable assumption in wide vessels but in small vessels there is a tendency to greater turbulence and a wider range of velocities (Leech 1988).

Optimal conditions for the measurement of diameters and velocity integrals differ. Axial resolution is superior to lateral resolution and so for diameter measurement it is preferable to have the vessel lying at right angles to the direction of insonation. For Doppler recordings, on the other hand, a vessel lying parallel to the ultrasonic beam is preferable since θ is reduced. Thus it may be extremely difficult to measure both variables accurately with the fetus in any one position.

The ability to measure, reproducibly, volume flow in the fetal heart would be of great clinical value. Our findings cast doubt on the ability of combined cross-sectional and Doppler ultrasound to estimate volume flow in the fetal heart. We have demonstrated that this imprecision arose most seriously from technical difficulties in measuring fetal heart diameters. In addition there was uncertainty about the reliability of Doppler measurements in the fetal heart.

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Symptoms analysis for the diagnosis of genuine stress incontinence

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Abstract

Objective—To determine the accuracy of an analysis of symptoms alone for the diagnosis of genuine stress incontinence.

Design—A comparison of results of symptoms analysis with urodynamic findings

Setting—A gynaecological video-urodynamic unit.

Subjects—252 consecutive patients referred for urodynamic investigations.

Interventions—A questionnaire of 20 symptoms of lower urinary tract dysfunction, midstream specimen of urine, pad testing, uroflowmetry, and videocystourethrography

Main Outcome Measures—Using the urodynamic diagnosis as the 'gold standard', the accuracy of discriminant function analysis of symptoms was determined.

Results—Symptoms analysis achieved a correct classification of 81% with a false positive rate of 16%. Use of an accumulative probability curve defines patients who fall into the equivocal range.

Conclusions—All women presenting with incontinence should undergo pre-operative urodynamic studies.

Genuine stress incontinence (GSI) is the most common cause of urinary incontinence in women and its definitive treatment is bladder neck surgery. It is essential to arrive at the correct diagnosis before surgery as the consequences of misdiagnosis are irreparable.

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Unfortunately, diagnoses based on symptoms alone are frequently incorrect (Jarvis *et al* 1980; Cardozo & Stanton 1980, Shepherd *et al* 1982; Frazer *et al* 1987) and so urodynamic studies have been advocated for patients with mixed symptomatology. An audit of the symptomatology in women attending a urodynamic clinic revealed that only 2.4% of them complained of stress incontinence alone and so the vast majority of patients had mixed symptomatology (Haylen & Frazer 1987). At present there exists no rational and reproducible basis on which to found a policy for referral for urodynamic studies and so it would appear that all patients complaining of incontinence should be investigated before treatment. These studies are expensive in terms of equipment and staff expertise and so any method whereby the number of urodynamic referrals could be limited would be a cost-saving exercise

The aim of this study was to determine whether all women with the symptom of stress

incontinence require urodynamic investigations before surgery. It has been argued that studies demonstrating the weakness of clinical methods of diagnosis (see above) may merely have demonstrated the weakness of the clinicians concerned. Such criticisms are difficult to refute as clinical judgement is a 'moveable feast'. To obviate such criticism, the effect of the 'human factor' has been reduced in this study, by use of a computer to determine the clinical diagnosis. This has been achieved by employing discriminant analysis on the symptoms data. This technique employs a mathematical model to differentiate patients with urethral sphincter weakness from those with intact sphincters on the basis of symptoms alone. Because it is a computer model, it is totally reproducible unlike the clinical judgement of physicians. The accuracy of this computer-based diagnosis has then been assessed against the results of pad testing (Versi & Cardozo 1986), videocystourethrography (VCU) (Bates *et al.* 1970) and uroflowmetry which have acted as the 'gold standard' for comparison. On this basis the accuracy of symptoms alone has been computed.

Subjects and methods

Patients referred for urodynamic investigations were recruited for the study. Of 252 consecutive patients studied with a urodynamic diagnosis, only 30 (12%) had had prior referral for lower urinary tract dysfunction and so in the main this population was not adulterated by treatment failures. This was because the unit acted essentially as a primary referral centre. Assessment consisted of patients being asked 20 questions, concerning the symptoms listed in Table 1, by a gynaecologist (E.V.) and the responses were coded as: 0 = none; 1 = occasional; and 2 = frequent for all symptoms listed in Table 1 except for frequency and nocturia where the responses ranged from 0 to 7. For diurnal frequency this was a coding to represent severity of symptoms such that a score of 5 or more implied a frequency of greater than 8 times per day. Patients complaining of nocturia had the number of times per night recorded except when it exceeded 7 times in which case it was recorded as 7.

All patients had sterile urine (an inclusion criterion) as judged by the microbiology department on the basis of a midstream specimen of urine. Urodynamic investigation was carried out as follows. On arrival in the department patients

were given 500 ml of water or squash to drink as part of the pad test investigation (Versi & Cardozo 1986). After the pad test exercise regimen, the pad weight was recorded and then the patients were asked to void on the flowmeter, and the peak flow rate and the volume voided were measured. This was followed by catheterization and subtracted provocative fluid fill cystometry. A VCU was recorded as described by Bates *et al.* (1970). The diagnosis of GSI was made when the pad test was positive (>1 g increase) and there was evidence of urethral sphincter incompetence during the VCU study. That is on coughing, contrast medium was seen to streak past the mid urethra in the absence of abnormal detrusor activity.

All terms, methods, definitions and units conform to the standards recommended by the International Continence Society except where specifically noted (Abrams *et al.* 1990)

Analysis

The symptoms information was formatted using a SPSS-X package (Norusis 1975) and the data were subjected to discriminant analysis for classification purposes. Using the direct method of classification with discriminant analysis (Klecka 1987), a discriminant score (F) was obtained:

$$F = aA + bB + cC + \dots + vV$$

where A, B, C etc., represented the value for each of the 20 symptoms and a, b, c etc., their

Table 1. List of symptoms used in the questionnaire

Incontinence	Stress incontinence
	Urge incontinence
	Wet at rest
	Wet on standing
	Wet at night
	Unaware of wetness
	Post-micturition dribble
Frequency	Protective pads and pants
	Diurnal
	Nocturnal
Sensation	Urgency
	Unaware of bladder fullness
	Perineal discomfort
	Pain on micturition
Flow	Poor stream
	Incomplete emptying
	Strain to void
	Unable to interrupt flow
Neurological	Leg weakness
	Rectal soiling

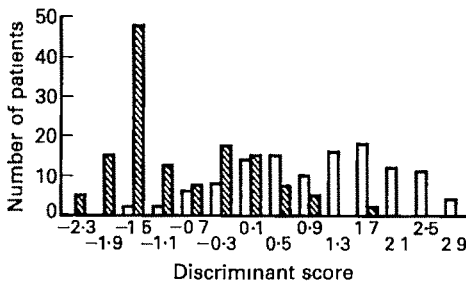


Fig. 1. The histogram shows the distribution of discriminant scores in patients with genuine stress incontinence (□) and in those who have an intact sphincter (▨). Note that although women with an intact sphincter have a lower score, there is still too much overlap to allow this technique to be used diagnostically.

coefficients. This statistical technique computes these coefficients and so weights the importance of any given symptom to obtain the greatest possible discrimination between patients with urethral sphincter incompetence and those without. Using the urodynamic assessment as the gold standard, patients were classed as having GSI (sphincter incompetence) or not having GSI (sphincter competence). Patients with GSI concomitant with other urodynamic conditions were classed as sphincter incompetent. Figure 1 shows the distribution of discriminant scores for patients with and without GSI. On the basis of the discriminant score derived from the symptoms, it is theoretically possible, to classify patients into two groups (sphincter continent and incontinent). The fact that the symptom scores cannot be said to be normally distributed makes little difference to the classification analysis as this technique is very robust (Lachenbruch 1975).

Table 2 shows the diagnosis based on the dis-

Table 2. A comparison of the diagnosis based on symptoms analysis with those that were found on urodynamic testing

Urodynamic diagnosis	Discriminant function diagnosis		Total
	Sphincter incompetent	Sphincter competent	
GSI	92	26	118
No GSI	21	113	134
Total	113	139	252

GSI = genuine stress incontinence.

kappa = 0.62

criminant score compared with the urodynamic diagnosis. Kappa (Cohen 1968; Landis & Koch 1977) is a statistical parameter used to compare the agreement between tests and is calculated as follows:

$$K = (Po - Pe)/(1 - Pe)$$

where:

P = (true positives + true negatives) divided by the total number.

Po = observed proportion of agreement.

Pe = expected proportion of agreement.

Figure 2 is a computation of the cumulative probability of GSI for any given discriminant score (F). This probability plot has been constructed from the data in Fig. 1.

Results

Figure 1 shows that the discriminant score cannot be used to diagnose GSI reliably as the overlap between the two groups (GSI and normal) is too great. Quantification of the accuracy of the symptoms score analysis is shown in Table 2. There was a correct classification of 81% with a false positive rate of 16% and a false negative rate of 22%. Comparing the discriminant diagnosis (symptoms) with the urodynamic diagnosis yields a kappa value of 0.62 which would suggest a 'substantial' degree of concurrence (Landis & Koch, 1977). However, a sensitivity of 78% and false positive rate of 16% are unlikely to be an acceptable level of accuracy. For this data set, Figure 2 enables the probability of urethral sphincter incompetence to be determined from any discriminant score. For example from the

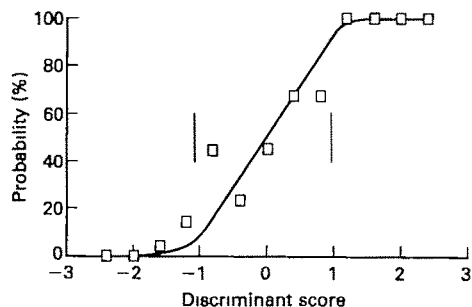


Fig. 2. The sigmoid curve is a probability function derived from the data in Figure 1. From the graph, given a symptoms discriminant score for any patient, the probability of a diagnosis of genuine stress incontinence can be read. The bars denote the equivocal range.

graph it can be deduced that a patient's symptom discriminant score of >1.2 would suggest a probability of urethral sphincter incompetence of over 95%.

Discussion

Given that most patients with urinary incontinence display mixed symptomatology (Haylen & Frazer 1987) the clinician has mentally to weigh up the importance of any given symptom. The clinical diagnostic process then takes this information and uses it in combination with the physical signs to provide a final diagnosis. Unfortunately the sign of stress incontinence is not always elicited as incontinent patients tend to present to office or out-patients departments with an empty bladder and are examined in the supine or lateral position. Also it is possible that leakage per urethram is not perceived in women with urethral sphincter incompetence but may be in some with detrusor instability. Therefore the history is the most important component of the clinical picture.

Clinical judgement in weighing up the significance of different symptoms is not very reproducible between different clinicians and so this may explain why the clinical diagnosis corresponds poorly with the urodynamic diagnosis (Jarvis *et al.* 1980; Shepherd *et al.* 1982). Re-analysis of these published data for concordance yields a kappa value of 0.41 for the data from Jarvis *et al.* (1980). These previously reported studies relied upon the clinician's judgement and so to reduce the inter- and intra-observer error, the analysis in this paper has used defined levels of symptom intensity (none, occasional or frequent) and employed a computer (discriminant analysis) to weight the importance of the symptoms. This replacement of 'man by machine' results in reduced flexibility but greater reproducibility. Thus the concordance between symptoms diagnosis and urodynamic diagnosis is greater and more reproducible using the computer giving a kappa value of 0.62 ± 0.03 . This level of kappa implies 'substantial' agreement (Landis & Koch 1977).

A diagnosis of sphincter incompetence or otherwise was made in 205 of 252 patients on the basis of symptoms alone. This resulted in a correct classification in 81% using the urodynamic diagnosis as the gold standard. However, a sensitivity of 78% is inadequate because if the decision to operate was based on this infor-

mation 21 patients or 8% of the 252 would have undergone an unnecessary and possibly harmful operation (Table 2).

Figure 2 would be generally applicable for the age range of patients in the data set if the prevalence of GSI in the incontinent population at large was similar to our urodynamic clinic population. It is unlikely that this assumption is tenable given that our patient population consisted of patients referred specifically for urodynamic studies. From Fig. 1 it can be seen that no cut-off point can be chosen on the range of discriminant scores to reliably separate patients with an intact sphincter from those with sphincter incompetence. It is, however, possible to define equivocal cases on the basis of the discriminant score. Those patients on the extreme left of Fig. 2 (negative scores) are likely to have an intact sphincter while those on the extreme right (positive scores) are likely to have sphincter incompetence. The patients which fall in the middle of Fig. 2 (steep part of the slope) could be classed as equivocal. The larger the range of discriminant scores classed as equivocal (between the bars in Fig. 2), the greater would be the accuracy. However, such increase in accuracy would be at the cost of fewer patients being diagnosed. Therefore by adjustment of the equivocal range, the desired accuracy could be achieved. For example, given a 5% permissible error it could be stated that the 61 patients with a score of <1.4 would have an intact sphincter and so would not require surgery. Similarly the 44 patients with scores of >1.5 would be likely to have an incompetent sphincter and so may require surgery.

This system would result in patients with a mixed condition (GSI + other pathology) undergoing bladder neck surgery. To avoid this, pre-operative cystometry to identify patients with detrusor instability or uroflowmetry to identify patients with voiding difficulties may then become necessary. Those patients with a discriminant score of <-1.4 (24%) should not undergo bladder neck surgery but may still require urodynamic assessment for diagnosis of their underlying condition. Thus, it can be demonstrated that even with the stringent symptoms analysis presented here, the need for urodynamic assessment is not obviated as it only results in a diagnosis in 42% of the patients (given a permissible error rate of 5%). In other words, a diagnosis cannot be established with any certainty on the basis of symptoms alone in 58% of patients. Perhaps this sort of analysis

could determine priority levels for patients awaiting urodynamic assessment. Also the type of urodynamic test could be decided on the basis of the result of this analysis.

The mathematics presented here are complicated and require the use of a computer. For the practising clinician this would not be necessary. The discriminant coefficients of the variables (symptoms) could be pre-programmed into a simple calculator so, for any given patient, the only calculation necessary would be the computation of the value of the discriminant score 'F' as defined in the equation in the methods section.

In the above discussion it has been assumed that the prevalence rates of the urodynamic pathologies are typical of the population at large. This assumption is clearly not tenable and extrapolations cannot be made to a geriatric population. Our urodynamic centre was a primary referral centre in that only 12% had received treatment for lower urinary tract dysfunction in the past. However, it is likely that the prevalence rates in general practice would be different so again extrapolation would be unrealistic.

In conclusion it can be stated that even with complicated analytical techniques such as discriminant analysis, symptoms alone cannot be used to determine accurately which patients require bladder neck surgery. These data and the analysis reinforce the assertion that the bladder is an 'unreliable witness' and so urodynamic studies are necessary for all patients presenting with symptoms of lower urinary tract dysfunction.

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Relation of fetal blood gases and data from computer-assisted analysis of fetal heart rate patterns in small for gestation fetuses

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Summary. Fetal heart rate (FHR) monitoring and computer-assisted analysis were performed immediately before cordocentesis in 25 severely small-for-gestational age fetuses. There were significant associations between FHR variation and both umbilical vein blood PO_2 ($r=0.66$) and pH ($r=0.69$). However, the wide scatter of values around the regression lines prevented accurate prediction of fetal blood gases from FHR patterns. Nevertheless, FHR variation <20 ms was always associated with severe fetal hypoxaemia and acidaemia.

Although fetal heart rate (FHR) monitoring is widely used in the assessment of fetal well-being, there is considerable intra- and inter-observer variation in the interpretation of the various patterns (Trimbos & Keirse 1978; Lotgering *et al.* 1982). Computerized analysis has been introduced with the aim of providing reproducible results. Smith *et al.* (1988) have demonstrated a significant association between FHR variation and umbilical cord blood PO_2 in samples obtained at elective caesarean section within 24 h of FHR monitoring (Dawes *et al.* 1985; Smith *et al.* 1988). However, the results of such studies might have been influenced by the delay between FHR analysis and blood sampling as well as the possible effects on blood gas data of

maternal pre-oxygenation, anaesthesia or surgery.

With the introduction of cordocentesis it has become possible to examine the relation between FHR patterns and umbilical cord blood gases *in utero* (Nicolaides *et al.* 1986).

Subjects and methods

The FHR was monitored immediately before cordocentesis in 25 pregnant women who were referred to our unit for further investigations at 28-39 (mean 31.5) weeks gestation because of suspected severe intrauterine growth retardation. Gestational age was determined by Naegele's rule. The fetal abdominal circumference was 2.3-8.7 SD (mean 5.6 SD) below the normal mean for gestation of our reference range. Amniotic fluid volume was assessed subjectively by ultrasonography and was normal in seven and reduced in 18; in 9 of the latter there was oligohydramnios. Subsequently, the birthweight of all infants was found to be below the 5th centile for sex and gestation (Fig. 1; Yudkin *et al.* 1987). All fetuses included in this study were chromosomally and morphologically normal. All women gave informed consent and the project was approved by the hospital ethics committee.

FHR recordings were made for 60 minutes

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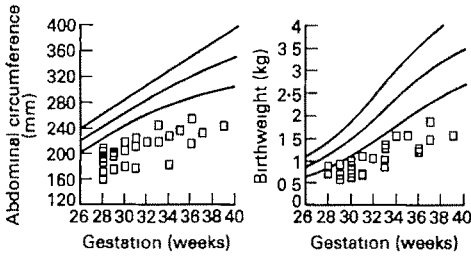


Fig. 1. Abdominal circumference of 25 SGA fetuses plotted on our reference range (mean, 95th and 5th centiles) for gestation (left). The birthweight is plotted on the reference range (mean, 95th and 5th centiles) for gestation from Yudkin *et al.* (1987) (right)

with the women in a semi-recumbent position (Hewlett Packard 8041A Cardiotocograph, Boblingen, West Germany). The System 8000 computer program (Sonicaid Ltd, Chichester) was used for analysis of the FHR traces. FHR variation was measured by averaging the one-minute ranges of pulse intervals about the baseline (mean minute range in ms) and the number of accelerations (amplitude >10 beats/min and duration ≥ 15 s) and decelerations (amplitude >20 beats/min and duration ≥ 30 s) was calculated. When large decelerations and accelerations were absent, smaller decelerations (≥ 10 beats/min, >60 s) were also identified. Since in 95–97% of normal third trimester fetuses the FHR variation is >30 ms, this value was taken to be the lower limit of normality for our study (Dawes *et al.* 1985).

Cordocentesis was performed as an outpatient procedure without maternal fasting, sedation or fetal paralysis (Nicolaidis *et al.* 1986). The cord vessel sampled was identified as artery or vein by the ultrasonic detection of the turbulence produced after the intravascular injection of normal

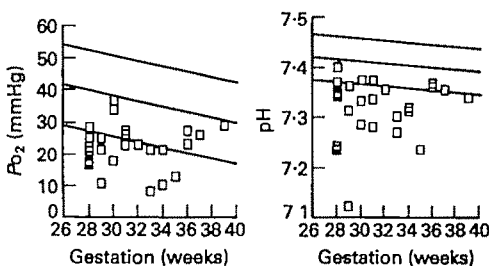


Fig. 2. Umbilical vein (UV) blood PO_2 (left) and pH (right) of 25 SGA fetuses plotted on our reference ranges (mean, 95th and 5th centiles) for gestation.

saline (400 μ l). In this study, only pregnancies in which the umbilical vein was sampled were included. Fetal blood (200 μ l) was aspirated into heparinized syringes and blood gas measurements used a Radiometer ABL 330 analyzer (Copenhagen, Denmark). The fetal temperature was assumed to be 37°C (Soothill *et al.* 1987).

Since in normal pregnancy the umbilical vein blood PO_2 and pH decrease with gestation (Nicolaidis *et al.* 1989a), the results for the small for gestational age (SGA) fetuses were expressed as the number of SD by which the measured values differed from the appropriate normal mean for gestation (delta PO_2 and delta pH respectively in SDs). Regression analysis and unpaired Student's *t*-test were used to determine the significance of the relation between FHR variables and delta PO_2 , or delta pH.

Results

In this group of 25 SGA fetuses, the mean PO_2 was 2.0 SD (range 0.2–3.7 SD) and the mean pH 3.4 SD (range 0.7–10.7 SD) below the respective normal mean for gestation (Fig. 2). In 20 (80%) of the fetuses the PO_2 and/or pH were below the 5th centile for gestation. FHR variation was significantly associated with both delta PO_2 ($n=25$, $r=0.66$, $p<0.05$, Fig. 3) and delta pH ($r=0.69$, $p<0.05$; Fig. 4).

Accelerations were absent in four (16%) of the FHR traces and both the mean delta PO_2 (-3.42 SD) and the mean delta pH (-6.12 SD) of this group of fetuses were significantly lower than in the 21 fetuses with accelerations (mean delta $PO_2 = -1.69$ SD, $t = -4.21$, $P<0.001$ and mean delta pH $= -2.85$ SD, $t = -3.27$, $P<0.01$).

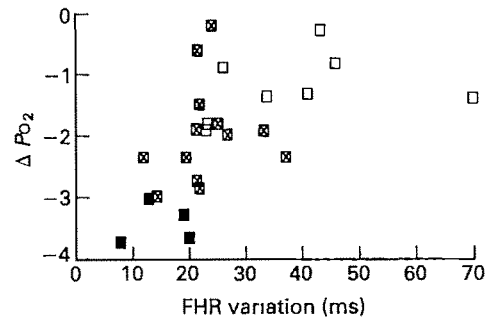


Fig. 3. Relation of fetal heart rate (FHR) variation and umbilical vein blood ΔPO_2 in 25 SGA fetuses
 □ = decelerations absent + accelerations present;
 ◻+ = decelerations + accelerations present;
 ■ = decelerations present + accelerations absent

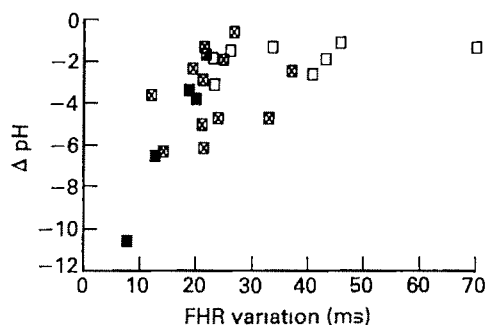


Fig. 4. Relation of fetal heart rate variation and umbilical vein blood Δ pH in 25 SGA fetuses.

□=decelerations absent + accelerations present;
 ⊠=decelerations + accelerations present,
 ■=decelerations present + accelerations absent.

Large decelerations were present in 12 (48%) of the FHR traces and the mean delta pH of this group of fetuses was significantly lower than in the group without decelerations (mean difference = -1.82 SD, $t=2.13$, $P<0.05$); the mean delta P_{O_2} was not significantly different in the two groups (mean difference = -0.60 SD, $t=-1.56$). When small decelerations were included both the mean delta P_{O_2} and mean delta pH were found to be significantly lower in the 17 fetuses with decelerations than in the eight without (delta P_{O_2} : mean difference = -1.08 SD, $t=-2.92$, $P<0.01$; delta pH: mean difference = -2.14 SD, $t=-2.39$, $P<0.05$).

In the six fetuses with FHR variation <20 ms, both the P_{O_2} and pH were below the 5th centile of the respective normal ranges; in all of them there were decelerations. In 10 of the 12 (83%) fetuses with variation 20–30 ms, the P_{O_2} and/or pH were below the 5th centile. In four of the seven (57%) fetuses with variation >30 ms, the P_{O_2} and/or pH were below the 5th centile, two of these fetuses had decelerations. For variation <30 ms, the presence or absence of decelerations or accelerations did not improve the prediction of blood gas results.

Discussion

In this group of severely growth retarded fetuses, 80% were hypoxaemic or acidaemic or both. Fetuses with either reduced FHR variation, decelerations or absence of accelerations were significantly more hypoxaemic and acidaemic than those with no FHR abnormalities. These findings are compatible with previous studies where FHR patterns were analysed

visually and the results were related to pregnancy outcome or blood gas values in labour, at birth or at cordocentesis (Visser & Huisjes 1977; Nicolaides *et al.* 1989b; Visser *et al.* 1990). In this study the FHR patterns were not examined in relation to pregnancy outcome because the time and mode of delivery were largely based on blood gas results at cordocentesis.

Computerized analysis has made it possible to quantify FHR patterns accurately (Henson *et al.* 1983; Dawes *et al.* 1985). In the present study there were significant associations between FHR variation and umbilical vein blood P_{O_2} or pH (Figs. 3 and 4). The association between FHR variation and blood P_{O_2} is similar to that reported by Smith *et al.* (1988) who studied samples obtained from the umbilical cord at elective caesarean section. In contrast, neither Smith *et al.* (1988) nor Henson *et al.* (1983) found a significant association between FHR variation and umbilical artery pH in samples obtained at caesarean section in a heterogeneous group of high risk pregnancies (Henson *et al.* 1983; Smith *et al.* 1988). Indeed, these authors suggested that the reduced FHR variation in compromised fetuses is not the direct result of acidaemia but of hypoxaemia or some other factor associated with growth retardation. The most likely explanation for this apparent discrepancy in results is the fetal blood vessel sampled. Although umbilical artery blood may indeed be more representative of the 'fetal condition' (Henson *et al.* 1983), the activity of peripheral chemoreceptors, possible cardiac centres in the brain and the heart itself are more likely to be influenced by the composition of umbilical vein than artery blood. An additional explanation is the difference in the definition of acidaemia. Smith *et al.* (1988) and Henson *et al.* (1983) considered acidaemia to be present if the pH was below a certain fixed value irrespective of gestation whereas in the present study acidaemia was defined as a pH value below the fifth centile of a normal range that changes with gestation.

Computer-assisted analysis of FHR patterns provided reproducible numerical data that were related to indices of fetal oxygenation. FHR variation <20 ms was always associated with severe hypoxaemia and acidaemia whereas variation >30 ms was suggestive of normal blood gas results when decelerations were absent. However, when FHR variations were between 20 and 30 ms, the large scatter in values did not enable

accurate prediction of fetal PO_2 or pH, even when presence or absence of decelerations and accelerations was taken into account.

The 'scatter' of values around the regression lines describing the relations between FHR patterns and PO_2 or pH (Figs. 3 and 4) could be a consequence of the independent or additional effects of the deranged endocrinology and metabolism found in growth retarded fetuses (Robinson *et al.* 1979; Nicolaides *et al.* 1989c). Furthermore, the scatter in values may be due to the biological variation both in responsiveness to intrauterine stress and in inherent FHR patterns. Support for the latter is provided by Smith *et al.* (1987) who examined a group of normal fetuses with low FHR variation and demonstrated that perinatal outcome was normal despite persistence of low variation throughout the third trimester of pregnancy.

Our data suggest that in SGA fetuses, FHR variation <20 ms reflects severe hypoxaemia and acidaemia. But, the clinical significance of FHR variation >20 ms can only be determined by further assessment, such as sequential FHR monitoring, which may identify further responses to deteriorating intrauterine conditions (Snijders *et al.* 1989). Alternatively, other non-invasive tests, or cordocentesis are needed.

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Computerization of a colposcopy clinic

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Summary. The first phase of a paperless computer record has been developed at Hammersmith Hospital. The system was designed around the work practices of the clinic staff. In this phase the data are collected on forms which replace the normal case notes. This information is entered onto an IBM compatible computer by the secretary using a quick, user-friendly program written in a dBASE dialect and compiled with Quicksilver. The program produces letters to patients and their doctors and a printed record of the clinic findings for the case sheet to replace the handwritten form. When funding for hardware becomes available the data will be entered directly into the system by the medical staff in the clinic. Clinic appointment lists are maintained and patients 'lost to follow-up' can be identified. *Ad hoc* enquiries can be made using dBASE III Plus or any similar program. This approach has integrated the computerized recording of data in a colposcopy clinic with the normal work of the staff involved so that no extra effort is required from medical or secretarial staff. The immediate accessibility of patient data and the ability to audit the work of the clinic have been particularly useful.

Computerization of clinical data can provide important benefits (Gonzalez & Fox 1989) but there are several significant problems (Table 1).

The biggest difficulty is getting reliable information into the system in the first place. The system must allow the data to be collected during the normal working routine and must not make additional demands upon those who collect the information. It is essential that the system produces output which is useful to the users who enter data. Letters must appear natural and contain as much information as a dictated letter. Printed notes for the patient's case sheet must be in an easily readable form. If these principles are

not observed a large amount of information will never be recorded on the computer system. In one recent report in which data held in an established computerized audit system were checked against ward records, it was found that 30% of the data were missing from the computer database (Lyons & Gumpert, 1990). Less than half of this was recovered after intensive enquiry by a medical audit research coordinator.

Computerization has a special value in a colposcopy clinic because the women may have a premalignant or malignant condition. It is essential that the service is organized in such a way as to minimize the risk of test results going missing or being overlooked and of patients being lost to follow-up. Manual systems provide only limited protection, are labour intensive and difficult to monitor. A computerized system has the potential for overcoming these deficiencies and for providing the additional advantage of allowing an audit of the clinic's activities. This paper describes the development of such a system.

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Table 1. Benefits and difficulties in the computerization of clinical records**Benefits**

1. Guides new medical staff
2. Automates correspondence
3. Provides legible, printed case notes
4. Patient data are readily accessible
5. Appointments are made or changed more quickly
6. Lost results or defaulting patients are readily identified
7. Audit is simplified

Difficulties

1. Data must be collected from *every* patient
2. Data collection must be achieved without adding to the work load of clinical or secretarial staff
3. The system must bring tangible benefits to all the staff who enter data
4. The system must be suitable for staff who cannot type
5. The system must be easy and flexible in use
6. The cost of hardware and software and the development time must be acceptable
7. Modification of the system is often necessary to deal with different needs or in the light of experience

Methods**Objectives of the system**

The main objectives of the system were defined as follows: (i) ensure that clinical findings and test results are recorded, and that appropriate arrangements are made and carried out; (ii) reduce the work involved in correspondence; (iii) simplify the making and changing of appointments; (iv) provide a means of auditing the work of the clinic.

Requirements for the system

The following were considered essential: (i) no member of the clinic staff should have to undertake additional work in running the system; (ii) no member of staff should have to record the same data more than once; (iii) staff entering data into the system should see a tangible output from their effort.

System design**(a) Data input**

The referral letter provides the patient's name, date of birth and address, and the address of the referring doctor and of the general practitioner.

The history and clinical findings are recorded by medical staff on data forms instead of writing notes in the case sheet. There are separate forms for first visits, treatment visits and for follow-up visits. The doctor also records what tests have been performed and indicates the provisional plan of management.

The information on the form is entered into the computer by the secretary. Since the system provides letters automatically, this replaces the work of typing letters. She can create a new record to record data for the first time, amend details already entered, or merely enquire about the information in a way that does not allow alterations to be made (Fig. 1). There are separate series of data entry screens for first visits, treatment visits and for follow up visits. Each visit record is linked to a corresponding results record where the results of the tests and the arrangements for further management are entered.

When laboratory results (smear or biopsy) become available, the doctor adds these to the form and confirms the management plan. The secretary enters this new information on the computer using the results screen (Fig. 1). She then makes an appointment for the patient, using the built-in appointment diary, and prints out letters to the patient, to her general prac-

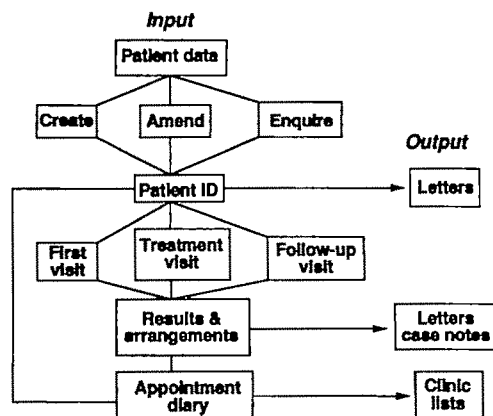


Fig. 1. Colposcopy program showing the flow of patient data through the separate modules of the system. The information may be created, amended or enquired upon. The correct patient is identified and information for a first visit, a treatment visit or a follow-up visit is recorded or inspected. Each of these visit records is linked to a record holding the results of the tests performed and the arrangements made for the patient. This is linked to the appointment diary. The output from the system consists of letters, clinic notes for the case sheet and clinic lists.

itioner and to any other doctor involved in her care (Fig. 2). At the same time, the data are printed out to replace the hand-completed form in the case notes after being checked and signed. Clinic lists can also be printed out when required.

(b) Data recording methods

Data items were categorized as either essential or non-essential. Essential data included any information required to enable appropriate management decisions to be taken, or which would be used in routine reports or future audit.

The essential data items were entered in a codified form so that they could be analyzed. This was achieved by presenting the user with a menu of choices and inviting the selection of one or more items from the menu (Fig. 3). The gynaecological history, the history of previous treatment to the cervix and clinical findings are among the data collected in this way. Very useful by-products of codification are the reduced demands on disc storage space and the improvement in data security.

In order to be able to record all the information the doctor wishes to enter, the scope of the data items must not be too restrictive. The relevant clinical findings may well include the results of pelvic examination or inspection of the vagina or the vulva in addition to the colposcopic examination of the cervix. Treatment of cervical disease might include laser therapy, diathermy, knife cone biopsy or hysterectomy. A substantial proportion of these patients might also need treatment of vaginal or vulval disease. All of these are recorded with single key-strokes selected from a menu. Error checking proce-

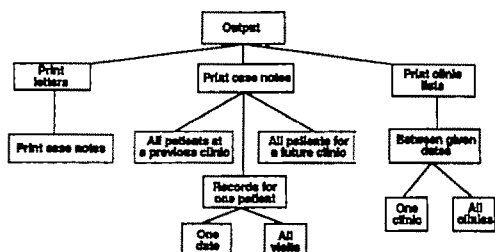


Fig. 2. Output from colposcopy program. The menu options available on the output menu allow the automatic generation of letters and case notes when the results and arrangements have been recorded. Case notes may also be printed by specific request as shown. The list of patients attending clinics are printed with comments about the clinic or about individual patients if required.

dures prevent the entry of a character not shown on the menu.

Non-essential data items are recorded to enable the medical staff to record on the computer all the information they collect so that they do not need to write a separate note in the case sheet as well. This is achieved by providing semi-structured, free-text entry fields with appropriate on-screen guidance (Fig. 4). The past and current medical history and the history of any drugs being taken or any drug allergies are some of the free-text entries.

Because the long-term aim is that the doctors should enter data directly into the computer in the clinic, the input is designed not to require a high level of keyboard skills. This is achieved by entering all essential items of information with a single character chosen from a menu displayed on screen.

(c) System output

So that medical staff do not have to write the same information again in the case notes, the system must be capable of printing out the recorded data for the case notes (Fig. 5). This is done after the test results and definite arrange-

Abnormalities seen on the cervix

Circle on the list below, any abnormalities noted. If you enter "O" for other, write a brief description.

- N = No abnormality seen
 - M = Metaplasia
 - A = Atrophic changes
 - C = Condylomatous warts
 - F = Flat warty change
 - T = Congenital transformation zone
 - 1 = CIN I
 - 2 = CIN II
 - 3 = CIN III
 - 4 = Microinvasion suspected
 - 5 = Stage Ib seen colposcopically
 - 6 = Clinically overt invasion
 - 7 = Adenocarcinoma suspected
 - 8 = Indecisive/unsatisfactory colposcopy
 - P = Post-hysterectomy—no cervix!
 - O = Other
- specify

Position of the squamo-columnar junction

Circle the relevant code.

- 1 = On the ectocervix
- 2 = Seen easily in the canal
- 3 = Hidden in the canal
- 0 = No cervix—previous hysterectomy

Fig. 3. A portion of the data collection form for menu entry of colposcopy findings.

[5] SYMPTOMS

Enter the date of onset and a description of up to four symptoms which you wish to record in detail. Write these briefly as you would wish them to appear in the case sheet.

1. Date of Onset
Description
2. Date of Onset
Description
3. Date of Onset
Description
4. Date of Onset
Description

Fig. 4. A portion of the data collection form for free-text entry of relevant symptoms.

ments for the patient are known. These printed notes for the case sheet are produced at the same time as the letters and are signed by the doctor responsible for collecting the data when signing the letters. In addition, because the system cannot record graphical information, the clinician can then copy to the printout any drawings he has made in the clinic which he wishes to include in his notes.

The system produces letters to the general practitioner and to any other referring doctor. The letters reproduce much of the detailed data collected in the clinic rather than being a standard letter with little information specific to his patient. Letters to the patients contain explanatory information reinforcing what has already been discussed in the clinic. All of the letters and forms for the case sheet are produced automatically and do not need to be enhanced or modified by a separate word-processing package.

Error checking is included in the choice of letters too. This avoids the risk of inappropriate letters being sent out or of inappropriate management being implemented.

A clinic diary records all the appointments. A comment area for each clinic allows relevant notes to be entered—for example the absence of a member of staff on holiday. Similarly, a note may be written about each patient with an appointment. A printout of the clinic diary is provided for staff in the clinic.

A list can be generated of patients who appear

to have been lost to follow-up or who have missing results. The system is sufficiently flexible to allow the generation of *ad hoc* enquiries when required. The system codes can be readily translated into ICD codes for Körner statistics.

Software

The program was written in dBASE using dBASE III Plus (Ashton-Tate (UK) Ltd, Maidenhead). This was much easier than trying to develop the database from scratch in a language like C. A further, major advantage of this approach was that users are able to make *ad hoc* enquiries using the interactive facilities of dBASE III or IV. In order to speed execution of the program and to make use of advanced features like windows, the program was compiled with Quicksilver (Wordtech Systems Inc, Orinda, California). By writing the program 'in house' it was possible to revise the program in the light of practical experience.

Hardware

The computer chosen to run the program is a 12MHz 80286 IBM compatible machine with a 40Mb hard disc and a tape drive for making daily backup copies of the database. The same computer is also used by the secretary for wordpro-

Dorothy I Dene B UNITHO 000001 NHS DOB 01/01/51
1 Dorset Rd Dorset Town DO1 1DD
GP Dr A. Dunnington 1 Ayr Road Ayrshire AA1 1AA
Referring consultant

First visit 08/07/88
Reason for referral Abnormal smear
Referral smear or biopsy Mild dyskaryosis
Smear history The date of the last normal smear was 1986 She had 3 previous normal smears Her smears were 3-5 years apart
Symptoms suggestive of cancer Post coital bleeding
Description of relevant symptoms
Two months ago history post coital bleeding
Pecity 4+2 Contraception Combined oral contraceptive LMP 16/6/88 Not pregnant
Menstrual history K = 05/30 regular normal loss
Previous cervical surgery Date Hospital Treatment
1979 Bowensons general Cryotherapy for an erosion

Relevant operations
1971 Right ovarian cystectomy
1981 Cystoceleomy

Relevant diseases
Current Asthma—severe in winter
Previous Hodgkin's Disease

Current drug history
Oral retinoid 4-5 times per day Prednisolone 5 mg daily
Allergies The patient has no allergies

Clinical findings at this visit
Vulva Condylomatous warts
Vagina Shown evidence of VAIN II and early changes consistent with HPV infection
Pelvic organs A blood uterus
Cervix Suspected microinvasion The squamocolumnar junction was easily visible in the cervix

Smear result Severe dyskaryosis
Histology of cervix CIN II
Histology of vagina VAIN II and early changes
Histology of vulva VIN II and lichen sclerosus et atrophicus
Date of next visit 18/07/88 Advice for laser treatment to the cervix under general anaesthesia, excision of the vulval lesion and laser treatment of the vagina

W P. Boulder MD MB, FRCOG

Fig. 5. An example of the clinic notes produce by the system for the case sheet. The diagram is redrawn by hand when the note is signed by the doctor.

cessing. When patients phone for information or to change appointments, it is easy to switch quickly from word processing to the colposcopy program and back again without shutting down either program. This is achieved with a multi-tasking program (Desqview 2.2—Quarterdeck Office Systems, Santa Monica, California) in combination with an expanded memory board.

Results and discussion

The system has now been in use since April 1988. Initially, its use was confined to two of the colposcopy sessions in Hammersmith Hospital to allow a settling-in period while bugs in the program and problems in the implementation could be identified and corrected. An enhanced version was installed in February 1989. This addressed the implementation problems that had emerged from the initial trial period.

The system consists of a suite of 20 database files and 22 index files. It is run by 18 compiled and linked dBASE programs. With 970 patients on file a record will be located in under 3 s. Typically, a new data screen will be presented in less than 2 s.

The data collection forms undoubtedly look intimidating at first but the medical staff soon become adept in their use and find that data recording is faster than traditional methods. In addition, the forms provide guidance for new staff and act as an *aide memoire* to experienced clinicians in collecting essential data. The information is often more legible than the clinician's usual handwriting!

Although the system cannot record diagrams, it takes only a moment to copy the drawing made of the cervix to the printed case notes before signing the printout and the letters generated. This is also an opportunity to add or copy any other brief comments which the program cannot include. Over 90% of the correspondence is produced by the program but there are still situations where an individual letter is preferable.

A major advantage has been the immediate accessibility of the patients' records and appointment details. When a patient phones to change

her appointment the secretary can locate her record in 30 seconds. A new appointment can then be provided and recorded within a further one minute. To allow this sort of enquiry, it has been particularly important for the secretary to be able to move quickly and easily between her word processing and the colposcopy program.

The ability to identify women lost to the system has been invaluable. Two searches performed 3 months apart identified several women who were in danger of being lost to follow up. The database has already proved useful in clinical audit and research, allowing the histological diagnosis based upon colposcopically directed punch biopsies to be compared with that made from the subsequent laser cone biopsy (Skehan *et al.* 1990). As a result, the management protocols in the clinic have been modified. The results of these changes will be monitored with the help of the program.

Conclusions

The introduction of information technology to a colposcopy clinic has proved to be valuable in managing the large amount of vital information generated and in reducing the risk of losing data or of patients being lost to follow up. Of particular importance has been the integration of the new system into established practices so that medical and secretarial staff are not being asked to undertake additional duties.

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Direct antenatal fetal electrocardiographic waveform analysis

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Abstract

Objective—To establish a technique for continuous recording of fetal electrocardiograms (ECG) for waveform analysis in the antenatal period

Design—Prospective descriptive study.

Setting—Fetal Medicine Unit, Queen Charlotte's and Chelsea Hospital, London, UK

Subjects—35 women undergoing antenatal fetal blood sampling

Interventions—One end of an insulated Cooner wire was attached to the sampling needle and the other to an automatic ECG-ST waveform analyser.

Main outcome measures—ECG signals were obtained with the needle in the fetal abdomen during intrahepatic umbilical vein sampling or aspiration of fetal urine but not when it was in the placental cord insertion.

Results—Continuous recording of the T/QRS ratio was obtained for a total of 166 min (mean 8 min per fetus) from 20 fetuses (16–38 weeks). The T/QRS ratio had no correlation with gestational age and fetal heart rate and was similar to values described in term fetuses in labour.

Conclusions—The technique described can identify ST waveform changes and may be useful in the investigation of fetal cardiac arrhythmias, intrauterine growth retardation and in monitoring fetal transfusions.

Fetal electrocardiograms (ECGs) have been obtained directly from the fetus in labour to assess fetal wellbeing. ECG waveform

abnormalities such as ST segment elevation and an increase in T wave height are associated with fetal hypoxaemia (Jenkins *et al.* 1986; Arulkumaran *et al.* 1990). In the antenatal period the fetal ECG has been indirectly obtained transabdominally but due to low signal to noise ratio, recordings have been adequate only for the measurement of R wave intervals and hence to compute the heart rate (Wheeler *et al.* 1978; Carter *et al.* 1980). However, the potential clinical value of waveform analysis has stimulated efforts to improve the antenatal detection of fetal ECG (Oostendorp *et al.* 1989). We describe preliminary experience with a new technique for direct recording of the fetal ECG and waveform analysis during the antenatal period.

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Subjects and methods

Thirty-five women with singleton pregnancies

between 16 and 39 weeks gestation, who were undergoing clinically indicated fetal blood sampling or aspiration of fetal urine, gave informed consent to inclusion in this study which was approved by the hospital ethics committee. The indications for fetal blood sampling (FBS) were the need for rapid karyotyping in 15 (10 for maternal age, three for obstructive uropathy and two for fetal growth retardation), Rh alloimmunization in 18 and autoimmune thrombocytopenia in two. Premedication or fetal paralysis was not used.

FBS was performed as described previously (Nicolini *et al.* 1990a) and a wire was clipped to the hub of the spinal needle. The teflon coated wire was 60 cm in length, 0.1 mm in diameter and was of stainless steel (Cooner Sales Inc., Chatworth, California). The other end was connected to the signal receiving socket of STAN—an ECG ST waveform and fetal heart rate monitor (Cinventa AB, Molndal, Sweden). Two adhesive skin electrodes on maternal thigh connected to the equipment acted as reference and ground electrodes. The ECG signal was fed to a small pre-amplifier near the subject and the amplified signal was passed to the STAN recorder through an isolation unit. The ECG signal was processed by the STAN recorder as described elsewhere (Lilja *et al.* 1988). The height of the T wave and the total height of the QRS complex were calculated from the average ECG complex based on 30 such complexes and the T/QRS ratio was printed on a recording paper run at 1 cm/min. The average fetal ECG was plotted in analog form at 2-min intervals along with the continuous fetal heart rate trace. The ECG signal was displayed on a screen allowing immediate identification of poor signal quality. The recordings were obtained only for the duration of the indicated procedure.

The purity and fetal source of blood samples was checked at the time by separate red cell volume distributions on a particle size analyser (Coulter Channelyzer C-256, Coulter Electronics, Luton, UK) and later confirmed by the Kleihauer-Betke test. The haematocrit in fetal blood was determined by a Coulter S plus counter. Blood gas analysis was performed on 250 µl of fetal blood collected into heparinized capillary tubes. Published normal ranges were used for blood gases (Soothil *et al.* 1986).

Results

It was not possible to obtain fetal ECG signals in

any of the five pregnancies in which the site of sampling was the umbilical vein at the placental cord insertion. Satisfactory signals without interference from the maternal ECG were obtained in 20 of 30 fetuses who had the needle passed via the anterior abdominal wall into the intrahepatic vein or the fetal bladder. There were no obvious maternal or fetal differences between those with and those without successful ECG recording. The fetal haematocrit was 13–38% (mean 22.5%) in Rh fetuses and normal in all other fetuses. No fetus was hypoxaemic nor acid-aemic. ECG waveform analysis was performed for a total of 166 min (range 2–20 min; mean 8 min) in the 20 fetuses. FHR ranged from 120 to 190 min. The mean T/QRS ratio ranged from 0.04 to 0.28 and did not correlate with gestation or FHR ($r = 0.06$ and 0.08 respectively (Pearson's correlation coefficient)).

Discussion

This study indicates that ECG signals can be obtained directly from the human fetus *in utero* without interference from maternal ECG signals provided the needle is in the fetus. The T/QRS ratios obtained were similar to those reported for term fetuses in labour (Lilja *et al.* 1988; Newbald *et al.* 1989; Arulkumaran *et al.* 1990).

In labour the ECG is measured differentially between one electrode attached to the fetal scalp and one skin electrode on the maternal thigh and a third electrode in contact with the cervix or amniotic fluid acting as a reference. This creates a unipolar ECG lead which identifies ST waveform changes along the Y axis (crown rump) and has been found to be optimal for T wave detection (Lindecrantz *et al.* 1988). Our preliminary observations suggest that satisfactory ECG complexes can be obtained with the needle inserted into the fetal abdominal wall and two skin electrodes attached to the maternal thigh. This arrangement appears to be adequate for identification of ST waveform changes but further studies are needed to establish this.

There are several possible clinical applications. Antenatal fetal blood sampling to assess acid base balance in growth retarded fetuses with abnormal blood velocity waveforms is of dubious value (Nicolini *et al.* 1990b). However, study of the ECG waveform (T/QRS ratio) and its relation to fetal acid/base status in compromised fetuses might improve the understanding of fetal adaptation to hypoxaemia and also might help in predicting perinatal outcome.

Intravascular transfusion has become the accepted therapy for fetal anaemia secondary to red cell alloimmunisation (Rodeck & Letsky 1989). During transfusion, the turbulent flow of blood in the umbilical vein is monitored with ultrasound in order to confirm correct needle placement. This cannot be done continuously as the ultrasound probe has to be moved intermittently to observe the fetal heart rate. The technique described here can record the heart rate from the ECG and would permit undivided sonographic attention to be given to the site of transfusion. Furthermore, analysis of the ECG waveform during transfusion could be of value in the early recognition of complications, such as cord haematoma and tamponade.

Finally direct fetal ECG analysis is likely to be of value in the investigation of fetal cardiac arrhythmias and in monitoring their therapy *in utero*. The method is greatly strengthened by the independence of the T/QRS ratio from gestational age and heart rate allowing its application in a variety of circumstances and for the results to be compared; but further technological development in the signal detection are needed in order to achieve a higher rate of successful recordings than that achieved in the present series.

Acknowledgments

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Difficulties in the diagnosis of congenital toxoplasmosis by cordocentesis. Case report

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Case report

A 28-year-old woman who booked at 17 weeks gestation had read about toxoplasmosis in a newspaper and wished to know her status with regard to this infection. After discussion of the limitations of serological testing and consideration of the potential sequelae, a sample of maternal blood was investigated for toxoplasma. Her serology indicated acute toxoplasmosis. Further questioning revealed a history of foreign travel 8 weeks before conception and a mild influenza-like illness at 6 weeks gestation. Ultrasound did not show any fetal abnormality and she chose to continue the pregnancy.

Amniocentesis at 20 weeks for isolation of *Toxoplasma gondii* by animal inoculation did not confirm fetal infection. The woman was given prophylactic spiramycin 3 g daily. At 23 weeks amniocentesis was repeated and cordocentesis was undertaken. The purity of fetal blood was confirmed by a Kleihauer test. In view of the positive fetal serology the woman was given alternating courses of spiramycin 3 g daily

for 21 days and a combination of pyrimethamine 25 mg/day, sulphadiazine 2 g/day and folinic acid 5 mg twice weekly for 21 days. This alternating antiparasitic therapy was continued until 38 weeks gestation when spontaneous labour ensued. A female infant was born by ventouse and there were no postnatal maternal complications.

The baby was born in good condition with Apgar scores of 9 at 1 min and 10 at 5 min. Her birthweight was 2800 g (10th centile), length 50 cm (50th centile) and head circumference 33 cm (10th centile). There were no clinical stigmata of congenital infection. A skull X-ray did not show intracranial calcification and liver function tests were normal. When the infant was 3 days old, a loud pan-systolic heart murmur was heard. Investigations revealed a ventricular septal defect of minimum clinical significance.

Because of the serological results the baby was treated for 3 weeks with spiramycin 100 mg/kg/day in two doses, and then for 6 weeks with a combination of pyrimethamine 1 mg/kg/day in two doses, sulphadiazine 200 mg twice daily and folinic acid, 5 mg twice weekly. Alternating courses of these drugs were given until the baby was 7 months old. During treatment with pyrimethamine white blood cell counts were checked weekly to detect bone marrow suppression. Mild leukopenia was noted, with the lowest neutrophil count being $0.88 \times 10^9/l$.

Regular clinical and ophthalmological follow-up of the child revealed no abnormality. When last seen, at the age of 7 months, her growth, developmental and ophthalmic assessments were normal.

Laboratory investigations

Toxoplasma-specific IgG was measured using the dye test, direct agglutination test and latex

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Table 1. Toxoplasma specific antibody findings in mother and infant

Serum sample	Dye test (IU)	Latex agglutination test (titre)	Direct agglutination test (units)	IgM ELISA (EIU)	IgM ISAGA (Index)
Maternal					
At 23 weeks	250	256	512	39 (Pos)	12 (Pos)
At delivery	125	256	—	69 (Pos)	12 (Pos)
Fetal					
At 23 weeks	31	16	128	5 (Neg)	11 (Pos)
At delivery	250	—	—	0 (Neg)	0 (Neg)
Infant (weeks)					
3	62	64	—	0 (Neg)	0 (Neg)
28	2	2	—	0 (Neg)	0 (Neg)
30	<2	<2	—	0 (Neg)	0 (Neg)

— = not performed

agglutination test (Johnson *et al.* 1989). Specific IgM estimation was by a double sandwich enzyme linked immunosorbent assay (DS-ELISA) and immunosorbent agglutination assay (ISAGA) (Duffy *et al.* 1989). Parasite isolation was attempted by intraperitoneal inoculation of laboratory mice. In addition, a recently developed DNA based assay was employed (Savva *et al.* 1990). Serological results are shown in Table 1 and parasite isolation and DNA probe findings in Table 2. Serological studies confirmed acute toxoplasma infection of the mother and specific IgM was detected in fetal blood obtained by cordocentesis. Toxoplasma-specific nucleic acid was detected in cord blood and placental tissue samples taken at delivery. However, DNA probe investigation of neonatal blood samples showed no evidence of infection of the child and serial assessment showed complete loss of passively acquired specific IgG by the age of 7 months.

Table 2. *Toxoplasma gondii* isolation results

Sample	Time of sampling (weeks gestation)	Animal inoculation	DNA probe
Amniotic fluid	20	Neg	Neg
Fetal blood	23	Neg	Not performed
Amniotic fluid	23	Neg	Neg
Placenta	At birth	Neg	Pos
Cord blood	At birth	Neg	Pos
Neonatal blood	At birth	Neg	Neg

Discussion

The management of *T. gondii* infection pregnancy includes maternal and fetal investigation, prophylactic and therapeutic antiparasitic treatment and also consideration of legal termination of pregnancy (Daffos *et al.* 1988). Calls for the introduction of routine antenatal screening for this infection and media interest have recently led to an increased demand for fetal assessment in cases of acute maternal toxoplasmosis (Joynson & Payne 1988).

If antenatal therapy is to be of benefit it is vital that fetal toxoplasmosis is diagnosed specifically. Congenital toxoplasmosis affects not only the newborn but can also result in severe visual impairment presenting late in childhood or during adult life.

Fetal blood sampling by cordocentesis is advocated for fetal assessment (Grose *et al.* 1989). Measurement of specific IgM in of fetal blood requires a highly sensitive and specific assay. Currently, the recommended technique is ISAGA which has shown to be significantly more sensitive than DS-ELISA with no difference in specificity. Using ISAGA, Daffos *et al.* (1988) detected specific IgM in fetal blood samples from 9 of 39 pregnancies where the infant was subsequently found to have congenital toxoplasmosis. The low sensitivity of IgM assessment was thought to be a result of the relative immaturity of the fetal immune system at the time of sampling and inhibition of IgM synthesis due to the suppressive effect of IgG passively transmitted from the mother. However, the specificity of ISAGA was reported to be absolute: no positive reactions in fetal samples

were ever associated with uninfected children (Daffos *et al.* 1988). Our finding of an ISAGA reactive blood sample taken from a uninfected infant may have been a false positive finding. This might have been the result of contamination of the fetal sample with maternal blood but Kleihauer testing did not reveal such contamination. The use of multiple tests to exclude maternal contamination of fetal blood samples has been suggested but this reduces the proportion of the sample available for diagnostic purposes (Forestier *et al.* 1988). A further explanation for our observation could be the transplacental passage of non-viable *T. gondii* leading to stimulation of the fetal immune system without an active disease process. Our experience indicates a need for caution when interpreting toxoplasma-specific IgM assays on fetal blood as ISAGA reactivity cannot be assumed to be an absolute indication of fetal infection. In our patient, the child received potentially toxic treatment and underwent extensive ophthalmic and paediatric follow up. In retrospect this management was unnecessary.

Of the many fetal blood investigations Daffos *et al.* (1988) claimed that parasite isolation had the greatest predictive value; they isolated *T. gondii* from 34 of 42 fetuses (64%) with congenital infection by inoculation of fetal blood and amniotic fluid in laboratory mice. This investigation must be continued for up to 45 days to achieve optimum results. As cordocentesis is performed at 20–24 weeks gestation, isolation of the parasite would involve consideration of a late termination. A reduction in the time required to generate diagnostic results would be advantageous. Tissue culture techniques could speed up diagnosis but they are less sensitive (Hughes *et al.* 1986). Preliminary studies have suggested that detection of toxoplasma-specific DNA in clinical samples may represent a rapid method of investigation with comparable or superior sensitivity to established methods (Savva *et al.* 1990). Cordocentesis yielded insufficient fetal blood to permit DNA investigation in our patient. However, neonatal blood contained no detectable toxoplasma DNA. The detection of toxoplasma DNA in concurrent samples of placenta and cord blood may represent maternal parasitaemia and contamination of these samples with maternal blood. Failure to isolate the parasite following animal inoculation of cord blood and placental tissue may represent lower sensitivity of this technique compared

with DNA detection. False positive reactions using the DNA probe method have not been reported (Savva *et al.* 1990). Isolated infection of the placenta without passage of the parasite to the infant has been noted, particularly after spiramycin treatment of the mother (Couvreur *et al.* 1988) and could account for our observations.

The case described illustrates the complexity of the diagnosis and management of toxoplasmosis in pregnancy and the need for an integrated multi-disciplinary approach to achieve optimum care of the patient.

Acknowledgments

Part of this work was funded by the Medical Research Council (R.E.H., D.S.). We are most grateful to Mrs I. Crossman for the preparation of this manuscript.

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SHORT COMMUNICATION

CA 125 and preterm prelabour rupture of the membranes

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Conservative (expectant) management of preterm prelabour rupture of the membranes (PPROM) is often undertaken in the knowledge that perinatal deaths from immaturity exceed those from infection (Daikoku *et al.* 1981). There is, however, the risk that amnionitis may develop and this has been estimated to occur in 60-65% of cases (Hawrylyshyn *et al.* 1983; Ismail *et al.* 1985; Fisk *et al.* 1987). Clinical signs are usually a late development, and the ESR and white cell count are of little clinical value. Although there is a significant association between elevated C-reactive protein (CRP) levels, clinical amnionitis and histological amnionitis, its usefulness is limited by lack of sensitivity and overlap between affected and non-affected cases (Fisk *et al.* 1987).

CA 125 is a tumour antigen identified by monoclonal antibody OC-125 and has been extensively studied in the diagnosis and monitoring of ovarian epithelial carcinoma. It has also been found in endometrium and decidua. High levels are found in the decidua and amniotic fluid in early pregnancy, with consequently high serum levels, which return to non-pregnant levels by the second trimester (Jacobs *et al.* 1988, Haga *et al.* 1986). CA 125 is elevated in patients with proven pelvic inflammatory disease (PID), and falls during antibiotic treatment (Paavonen *et al.* 1989). CA 125 can be localized immunohistochemically to reactive mesothelial cells in areas of inflammation and adhesions, and in pregnancy to the amniotic membrane and

amniotic fluid (Hahla *et al.* 1986; Nanbu *et al.* 1989).

It was hypothesized that as CA 125 was known to be present in normal decidua and amnion, and raised levels have been associated with other forms of pelvic infection, that it might be of value as a marker for amnionitis in PPROM. It seemed logical that this might be more sensitive than CRP, which is less specifically related to the tissues which are actually involved in amnionitis. There are no published data using CA 125 in this way.

Subjects and methods

A prospective blind pilot study was conducted. Daily serum CA 125 and CRP levels were measured in women after 26 weeks gestation with confirmed PPROM in whom conservative management was already indicated, until delivery. Those with clinical signs of infection at the time of PPROM were excluded. The presence or absence of diffuse amnionitis was diagnosed histologically, using published criteria (Benirschke 1961). Results were not available to the clinicians. CA 125 was measured immunoradiometrically with a commercially available kit (Cancer Antigen CA 125, CIS (UK) Ltd.) using a gamma-counter (LKB 1277 Gamma Master). CRP was measured by rate nephelometry (Beckman Instruments Array Protein System). A CA 125 level of 35 U/ml and a CRP level of 20 mg/l were taken to be the upper limit of the normal range for our laboratory. The levels of CA 125 and CRP in the last sample before delivery were compared using the Mann-Whitney *U*-test.

Results

Seventeen women were screened, and 26 blood samples taken. The number of samples taken per woman varied between 1 and 7. Five women had histologically confirmed diffuse chorioamnionitis (29%) and in two of these neonatal infection was confirmed subsequently. In the last

Haematometra secondary to hormone replacement therapy. Case report

NICHOLAS MORRIS, NAZAR AMSO, PHILIP CHALK

Case report

The patient was a 63-year-old multiparous woman, who presented with lower abdominal pain and tenderness of 4 months duration. The patient's recent past medical history was that she had complained of lower back pain for several months. She was 11 years post-menopausal. A bone density scan revealed a density one standard deviation below normal for her age, and she was prescribed a combined hormone replacement preparation.

Two months after hormone therapy was started, she developed lower abdominal pain and was referred to a general surgeon. At that time, sigmoidoscopy and barium enema were normal, and no further action was taken. Two months after this, she continued to have abdominal pain and was admitted to hospital. She had not experienced a withdrawal bleed during these 4 months of treatment. She was found to be apyrexial and normotensive. Abdominal examination elicited tenderness in the supra pubic region. Vaginal examination revealed an atrophic vulva and vagina.

The cervix could not be identified. On bimanual examination, a cystic mass equivalent to a 12 week size gravid uterus was palpated. Abdominal and vaginal ultrasound scans were performed. These showed an enlarged uterus, measuring $12.6 \times 4.1 \times 7.6$ cm. The uterine cavity was distended and contained low level echoes, consistent with a haematometra. Both ovaries were normal in size and in appearance. The uterus was drained under general anaesthesia through the cervix, using direct vaginal

ultrasound guidance; 500 ml of altered blood was drained. A Foley's catheter and Yates' drain were placed inside the uterine cavity for 5 days, to maintain the patency of the cervical os. The patient was readmitted to hospital 3 weeks later, and a dilatation and curettage was performed. The findings showed that the uterus had returned to normal size and that the cervix remained patent. The histology of the endometrium confirmed fragments of inactive endometrium, with a mild to moderate inflammatory infiltrate. There was no evidence of malignancy. Several weeks later the cervix was tested by a metal sound and was found to be patent. She had since decided not to continue with hormone replacement therapy.

Discussion

Hormone replacement therapy is effective in the prevention of osteoporosis. However, it is most efficient in women who have had an early menopause or are less than 65 years old (Savvas *et al.* 1987). This patient was 63 years old, and was given hormone replacement therapy 11 years after the menopause because of her backache and to prevent osteoporosis.

Sadly no pelvic examination was performed before initiating the treatment and furthermore it took 4 months before the patient was referred to the gynaecology department.

Haematometra has been described as a complication of hormone replacement therapy following radiation for cervical cancer (Sauer 1988). The radiation treatment resulted in cervical stenosis and the consequent development of a haematometra. In the management of this patient, the vaginal ultrasound demonstrated not only the distended corpus of the uterus, but also provided the safest point of entry into the cervical canal. This reduced the risk of perforation to bladder, bowel or blood vessels. Weinstein (1987) considered that continuous

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oestrogen and progestogen therapy was a better method of hormone replacement for women at risk of cervical stenosis. This treatment would result in the endometrium remaining atrophic and so bleeding would be minimal. This therapy should therefore be considered for women who not only have undergone surgery or radiotherapy to the cervix but also are started on treatment several years after the menopause

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CORRESPONDENCE

Patient selection for hysteroscopic endometrial resection

Dear Sir,

We would agree with Rutherford *et al.* [*Br J Obstet Gynaecol* (1991) **98**, 228-230] that the new minimally invasive methods of treating menstrual problems need careful assessment before their widespread introduction into clinical practice. This can only be done by a prospective randomized trial, as pointed out by Stirrat *et al.* (1990).

Both endometrial resection and laser ablation were introduced at Aberdeen Royal Infirmary at the beginning of 1990. After 6 months experience to obviate the problems of the 'learning curve', we commenced a randomized trial, funded by the Scottish Home and Health Department, comparing the two conservative procedures with hysterectomy in patients with a clinical diagnosis of dysfunctional uterine bleeding. This will avoid the problem of retrospective classification of the reason for operation, often not clearly recorded in the case notes, and we hope it will also identify predictive factors for success or failure of conservative treatment. Outcome will be measured not only in terms of symptomatic relief and complication rates, but by psychosocial changes and general health status. We aim to recruit around 250 patients over a 2-year period.

Of 71 patients recruited to date, 76% have significant dysmenorrhoea. Of 21 hysterectomies

on study patients, only 9 (43%) had no pathology at laparotomy. We hope to confirm or refute the suggestions made by Rutherford *et al.*, that these procedures should not be used in the presence of pathology such as fibroids or endometriosis, or where other symptoms, such as pain, are present. Whether endometrial ablation and resection can treat these women successfully is one of the many questions that need rigorous scientific assessment before the future role of these methods is clear.

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External cephalic version at term: how high are the stakes? Commentary

Dear Sir,

I fully agree with Dr Hofmeyr's [*Br J Obstet Gynaecol* (1991) **98**, 1-3] view that 'an attitude

of elegant distaste (for external cephalic version) is no longer tenable' in 1991.

Caesarean sections, in general, are used liberally in developed countries. This is because morbidity with abdominal delivery, even after repeated sections, is relatively low. This has

resulted in even more liberal use of caesarean section for breech presentation. Consequently the skills required both for external cephalic version (ECV) and vaginal breech delivery are scantily taught to a trainee in these countries.

The liberal use of caesarean section for breech presentation in developing countries, like India, can lead to many future obstetric problems. Most patients live in villages without immediate primary health care facilities. Due to lack of communication and poor transport they fail to reach the centre in reasonable time. Consequently the mortality and morbidity associated with either a breech presentation or caesarean section is much higher than has been recorded. By doing ECV at term, experience shows that these problems can be tackled to great extent.

In India, ECV is actively practised in some centres with great success, it is practised even when a woman is in labour with intact mem-

branes or following recent rupture of membranes early in the first stage of labour.

It has considerable potential for reducing both maternal morbidity and perinatal morbidity and mortality. The successful practice of ECV makes safer the future obstetric career of a woman in the developing countries.

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ADONIS 030654569100211U

The future obstetrician/gynaecologist. Commentary

Dear Sir,

I would like to write in support of Susan Bewley's leading article [*Br J Obstet Gynaecol* (1991) 98, 237-239]. It expresses a lot of what is currently wrong with training in the majority of hospital-based careers in medicine. Her proposal of a defined training period (although I think four years as she suggests is too short) must surely be the way forward. I suspect that as soon as one of the Colleges (whatever the speciality) has the foresight to implement such a training scheme, the others will be pressed to follow suite. The RCOG, which should be at the forefront of any proposal to encourage women to stay in a hospital-based career, ought to take steps to examine how such a scheme could be brought into being at the earliest opportunity.

P. M. Doyle

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Dear Sir,

I have just returned from the College, having attended the study day entitled 'Manpower and Achieving a Balance', where Dr Bewley repeated the views expressed in her commentary. She appears to see a shortened and more structured training programme as the answer to the ills of our speciality, as she perceives them. She suggests that a 4-year training would result in consultants being appointed at about 30 years of age.

Whilst I, at 32 years of age, would like to be a consultant now, instead of looking for a senior registrar post, and whilst I strongly support her ideas for a more structured training scheme, I do not see that shortening the training will bring our wishes to fruition.

The current College minimum training recommendations include: pre registration posts—1 year; SHO posts—2 years; elective year—1 year; post MRCOG training—3 years. This totals 7 years. Even with the addition of 2 years in 'research' this only totals 9 years. Why then do doctors, qualifying at the age of 23, take on aver-

age 14.5 years to obtain a consultant post (aged 37.5 years). What do we do for the extra 5½ years? Even a PhD would only take up 3 years. I suggest that shortening the training programme, in the current climate, to 4 years would result in trainees having to waste 10 years whilst waiting for a consultant post.

Surely the rate limiting step is the availability of consultant posts at the end of training. Equally then, having more doctors in consultant posts would be the best way to shorten the training time. To get more doctors in consultant posts we need primarily to press for further consultant expansion, but also to look at their working practice. Encouraging more job sharing posts at consultant level, and shortening the average working week would allow for an increase in the number of doctors in consultant posts.

A few years ago, the Duke of Edinburgh predicted that in order to deal with unemployment, the workforce would have to acclimatize to a much shorter average working week and much increased leisure time, resulting in a higher percentage of the population actually working for less time each. This would of course mean more pay for less work, in order to maintain sufficient income to live on and with which to enjoy the increased leisure time. I think I just saw a pig fly past the window!

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Dear Sir,

The leading recent article 'The future obstetrician/gynaecologist' by Susan Bewley fails to address the central problem of training in modern obstetrics and gynaecology, which is the issue of subspecialization.

It is no longer tenable that consultants should be expected to practise at the appropriate level

in the three major subspecialties of perinatal medicine, reproductive medicine, and gynaecological oncology. The clear identification of subspecialty interest after general training would significantly reduce the time needed in training. For example, practitioners wishing to concentrate on gynaecological oncology would not need to gain irrelevant extensive skills in amniocentesis, antenatal fetal monitoring, or the management of complicated obstetric cases. Similarly, individuals interested in reproductive medicine would not need to undertake the detailed surgical training required to be a proficient gynaecological oncologist.

The immediate introduction of subspecialization would significantly improve the quality of care to patients, improve the calibre of consultant consultations, and significantly reduce the training time. The expansion of consultant numbers with the introduction of shortened training programmes, enabling present day senior registrars to be considered as consultants, would easily permit the widespread application of subspecialization. Continuation of the excessively long training programmes, employed to produce amateur obstetrician/gynaecologists, provides inadequately trained consultants of great age. Neither medicine nor surgery require senior consultants to maintain equivalent skills in the broad range of their specialties, and it is time that obstetricians and gynaecologists admitted this fact in their own subject.

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Obstetric mortality and its causes in developing countries

Dear Sir,

Tom Barns' commentary [*Br J Obstet Gynaecol*

(1991) **98**, 345-348] was an excellent, succinct appraisal of the problem of maternal mortality in developing countries. I worked for two years in the Sahel of Northern Ghana where only 15% of

women were delivered within the hospital and maternal mortality for the hospital population was 17/1000.

The solution to the problem of maternal mortality appears daunting but should entail a three-fold approach.

1. Education for women, including literacy campaigns, has been shown to reduce maternal mortality more effectively than increasing medical personnel. Improving the status and socio-economic conditions of women reduces maternal and perinatal mortality. Educated women have fewer babies, take advantage of antenatal care, have improved pregnancy outcomes and less child mortality (Who 1985; Harrison 1985).

2. Appropriate education of health workers is essential and the overseas training of doctors may be unhelpful. Many do not return home and if they do they are often ill-equipped for their role as opinion leaders. The Diploma course at the Liverpool School of Tropical Medicine should be welcomed and its role in opinion forming not under-estimated. Midwifery training modelled on Western curricula is inappropriate for the many functions midwives are expected to fulfil whilst working in difficult, isolated conditions.

There may be a place for small, highly appropriate, local 'seminars' directed towards various grades of health worker involved in maternal care. These could be co-ordinated from 'an institute' which would also serve as a resource centre and a base for research into maternal health. It

would monitor the development of maternal health services, emphasize successful initiatives and co-ordinate its activities with other agencies. The International Centre for Eye Health at the Institute of Ophthalmology, London, provides a good example.

3. The extension of the nurse/midwife/medical assistant role could save lives in areas where it is difficult to attract adequate numbers of medical staff. Where I worked theatre nurses were able to perform caesarean sections satisfactorily but, officially, were prevented from doing so by the Nurses and Midwives' Council. At the same time the hospital was woefully understaffed with doctors. Part of the extended role could include prioritization and decision-making concerning the provision of appropriate community and hospital services.

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Conflicting views on the measurement of blood pressure in pregnancy

Dear Sir,

We were very interested to read the recent paper by Perry *et al.* [*Br J Obstet Gynaecol* (1991) **98**, 241-243] on the techniques used to record blood pressure in pregnancy in the Dudley Road Hospital, as we have carried out a similar but much larger survey in the Avon Health Districts (Bisson *et al.* 1990). We distributed 942 questionnaires to all general practitioners, hospital

obstetric staff, and hospital, community and student midwives in the three Avon Health Districts. Our response rate was similar (78%) as were many of our results; 42% of our participants continued to use phase 5 Korotkoff sound (compared with 53%), 70% recorded to the nearest 5 mmHg (compared with 66%), 23% recorded to the nearest 2 mmHg (compared with 10%) and 1.6% recorded to the nearest 10 mmHg (compared with 23%).

We were concerned about the apparent lack of

knowledge amongst the health workers about current recommendations for blood pressure measurement in pregnancy. We identified from our survey that the vast majority of antenatal blood pressures were taken by the midwives and we arranged ten blood pressure teaching sessions at the two maternity hospitals aimed at the community and hospital midwives.

Our questionnaire also included questions on the management of hypertension in pregnancy and the results showed an equally poor knowledge of the current recommendations (Bisson *et al.* 1991); this we consider to be of graver concern. Overall 93% of respondents considered oedema and 72% considered maternal weight gain as useful indicators in hypertensive disorders of pregnancy when neither have been shown to be of any prognostic significance (Friedman & Neff 1977; Campbell & MacGillivray 1975). In addition, 23% would restrict the patient's salt intake, 41% would recommend dieting and 3% would prescribe a diuretic, which have all been shown to be detrimental in pregnancy (Palomaki & Lindheimer 1970; Campbell & MacGillivray 1975, Redman 1989). We analysed our results according to the status of the health worker and found that the general practitioners were the group least well informed about current policies. The results of our study have been published in the British Journal of General Practice (Bisson *et al.*, 1991) and the management of hypertension in pregnancy has been included in the curriculum of the Avon GP Refresher Course.

We acknowledge that it is difficult to change views which are taught during training as if they were eternal verities but medical research serves no purpose unless the results are acted upon in clinical practice. We are hopeful that the steps we have taken will go some way to impart this important knowledge to the groups most in need of education

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BOOK REVIEWS

Midwifery Practice. Postnatal Care. A Research-Based Approach edited by Jo Alexander, Valerie Levy & Sarah Roch, Macmillan, Houndsmills, Basingstoke, 1990. 179 pages with figures and tables, Hardback £40, paperback £11.99.

This is the third in a series of books written for midwives and senior student midwives. The two books which precede it deal with antenatal and intrapartum care. The subjects covered by the contributors to this volume have been well chosen as representative of the wide spectrum of postnatal care. The quality is not always consistent but I would particularly recommend the chapters on breastfeeding, perineal care and teenage mothers.

Obstetricians should find this book useful both for themselves and for medical students and junior medical staff. It may be an easy way of introducing contemporary midwifery research and practice which is not routinely included in traditional medical textbooks.

The same format has been used throughout and is based on each chapter keeping to four main headings, plus references and suggestions for further reading. The authors state at the outset of the chapter their expectations of the reader's existing knowledge of the subject. The main body of the chapter then deals with a review of the research literature and concludes with recommendations for clinical practice. At the end of each chapter a comprehensive list of references is supplied. This form of presentation makes the book easy to search through and may be attractive to a busy practitioner.

In an area which has received perhaps less attention than other aspects of maternity care, resources such as this publication are helpful to all involved in the care of postnatal women and their families.

Sally Marchant

Medical Disorders During Pregnancy, edited by William M. Barron & Marshall D. Lindheimer,

Mosby-Year Book Inc/Wolfe Medical Publications, 1991. 647 pages with figures and tables, £57 00.

If responsibility for care during uncomplicated pregnancy returns to midwives and general practitioners, there is a danger that the obstetrician may become redundant if physicians continue to specialize in medical complications that arise during, or are complicated by, pregnancy. Only one chapter in this American text has been written solely by obstetricians (diabetes) and further evidence of the threat to obstetric isolation is the fact that each of the editors holds a position in 'Departments of Medicine and Obstetrics and Gynaecology'. These warning signs are not to be ignored if the specialist obstetrician of the future is to have a future. Clearly, obstetricians must show their willingness and ability to assume greater responsibility for medical complications during pregnancy and develop a rapport with physician colleagues. To this end, *Medical Disorders During Pregnancy* is worth more than just a fleeting glance.

Management of medical disorders during pregnancy has rarely been studied in a prospective controlled manner. Experience and observational studies form the basis of this excellent, and extensively referenced, text. Each chapter begins by emphasizing the need to understand the basic physiological and anatomical adaptations of the female body to the pregnant state. This is not any different in the USA and the fact that this is an American book is hardly noticeable. Thus, the book makes clear how knowledge of medical disorders must be adapted to, rather than superimposed upon, the changes of normal pregnancy.

Nineteen chapters address the main medical disorders that complicate, or are complicated by, pregnancy. In traditional American style, statistics abound but most of these are referenced so allowing verification of deviations from one's personal experience. In addition to the mainstay topics of hypertension, diabetes, infec-

tion, psychiatric disorders and diseases of the heart, lung, kidney, liver, endocrine glands, gastrointestinal tract, nervous system and skin, there are also chapters on critical illness, drug abuse, neoplastic disorders, and radiation exposure. Of particular value is the novel, single page, appendix which provides an index so that changes in laboratory values during pregnancy can be readily found in the text.

Seven contributors are British and three are French. The remaining 20 are from various parts of the USA. A clear and balanced view on most aspects of management is presented by way of deduction from the published literature. The contributors offer sensible interpretations of published experience tempered with appropriate comments that can only have been derived from their own respective, extensive, experiences. Recommendations are made but, by and large, this is not a book to turn to for a quick guide to management. Rather, it provides suitable background and reference reading to the subject.

Specialist obstetricians will enjoy this book which is a serious contender for a place on the personal bookshelf. *Medical Disorders During Pregnancy* will also appeal to physicians wishing to specialize in obstetric medicine. The book is easy to read, with two columns of text per page. Tables have been carefully selected to augment the text and the illustrations are clear and informative. By no means of least importance is the surprising fact that this high quality book is relatively inexpensive.

John A. D. Spencer

Micturition (Report of the 21st Study Group held at the RCOG October 1989), edited by J. O. Drife, P. Hilton & S. L. Stanton, Springer-Verlag, London, Berlin, Heidelberg, 1990. 356 pages, with figures and tables, £65.00

This book is published in conjunction with Springer-Verlag and is the result of the 21st Study Group, held at the Royal College of Obstetricians and Gynaecologists in October 1989. It is the third such study group concerned with urinary incontinence, the first having been published in 1981. Twenty-five international participants from the disciplines of gynaecology, general surgery, urology and basic sciences have contributed papers and provided fascinating even if obviously controversial discussion at the

end of many of the chapters. The usual spectrum of topics are covered with the emphasis, especially throughout the discussions on investigation and management which cause concern to the practising clinician.

Section headings include one on the basic sciences with up to date papers which are well referenced. The section on investigation obviously provoked considerable argument and discussion between the participants on the merits of various tests particularly that of urethral pressure profileometry. This section begins with a highly technical yet interesting account of the application of animal and physical models to the field of human cystometry. At a practical level the next three sections cover areas of considerable management problems to the practising gynaecologist and include a section on voiding difficulties, genuine stress incontinence and detrusor instability. The discussions which accompanied each of these sections were at times reassuring in that many aspects of the aetiology and management of urinary incontinence are still controversial. The last section on pelvic floor prolapse and the relation with the alimentary tract illustrate the increasingly recognized association between the development of vaginal prolapse and urinary incontinence.

This book is a timely contribution and provides a state of the art commentary on areas of the sub speciality of uro gynaecology

David Richmond

The No Hysterectomy Option. Your Body—Your Choice, by Herbert Goldfarb and Judieth Greif. John Wiley & Sons Inc., New York, Chichester, 1990, 265 pages, with figures and tables, £20.65

Much of the late 20th century, particularly in the USA, and now spreading here, has seen an explosion of advice largely in written form directed solely at our patients. One wonders whether the need for all these volumes is because doctors have lost the art of communication or are really too busy to listen and talk to their patients.

The No Hysterectomy Option is an American book written by a gynaecologist of considerable experience. He is helped in his writing by Nurse Judith Greif, (a curiously apt name for an author whose subject is hysterectomy).

There are chapters on 'Do you really need a Hysterectomy' where the advice to patients to

resist this operation is cogently put. The chapters on the physiology and anatomy of the female genital organs are clear. However there is a mistake here when the writer explains that the 'yellow' colour of the corpus luteum is due to cholesterol, pure cholesterol being white.

In the chapter on fibroids they seem to have rediscovered myomectomy and speak as if the operation had fallen from grace among American gynaecologists until quite recently. They also rightly criticize the D&C as a curative exercise and give the reader useful insight into new procedures such as hysteroscopy, endometrial resection and laser therapy. Medical methods of dealing with abnormal menstruation are covered with particular emphasis on the side effects of these drugs.

The American Fertility Society classification is described in detail but its failure to mention the 'qualitative' effects of this disease on the patient is a point that I had failed to appreciate before reading Dr Goldfarb. These authors subscribe to the view that episiotomy reduces the incidence of prolapse in later life but I know of no published work to support this. No-one ever taught me how to carry out 'an abbreviated pelvic examination' on a virginal adolescent patient but I am prepared to learn. Do American women really understand the meaning of 'Quantified digital radiography'? In a book directed at the sexually overstimulated USA I find the use of 'intimacy' for sexual intercourse both prissy and quaint.

The bibliography is large but has gaps where the author lacks enthusiasm for a subject. The 'Self-Help' addresses are unhelpful to a UK reader.

In conclusion although the book contains a few interesting nuggets for our patients its American orientation is so weighted that I would not recommend it to a British patient.

John McGarry

Books received some of which will be reviewed at a later date

Perinatal Haematological Problems (Perinatal Practice Volume 7) edited by Tom Turner. John Wiley & Sons, Chichester, New York, Brisbane, 1991. 240 pages with figures and tables, £45.00

A Colour Atlas of Childbirth and Obstetric Techniques edited by Farook Al-Azzawi. Wolfe Publishing Ltd, London, 1991. 144 pages fully illustrated with colour plates, £19.50

Year Book of Infertility 1990 edited by D. R. Mishell, C. Alvin Paulsen & R. A. Lobo. Mosby Year Book, St Louis, Baltimore, Boston, London, 1990. 251 pages with figures and tables £39.00

Prenatal Diagnosis of Foetal Malformations and Diseases Teaching Atlas of Amniofoetography by Lothar Abét, Peter Prenzlau & Johannes Richter. Akademie-Verlag, Berlin, 1991. 151 pages fully illustrated, 88 DM

Surgery at the District Hospital: Obstetrics, Gynaecology, Orthopaedics and Traumatology edited by John Cook, Balu Sankaran & Ambrose E. O. Wasunna. World Health Organization Geneva, 1991. 207 pages fully illustrated Sw fr 25, US\$22.50. In developing countries, Sw fr 17.50

The Human Embryo. Aristotle and the Arabic and European Traditions edited by G. R. Dunstan. University of Exeter Press, Exeter, 1990. 235 pages, illustrated, £25.00

Textbook of Gynecologic Oncology edited by G. P. R. Blackledge, J. A. Jordan & H. M. Shingleton. W. B. Saunders Company Ltd, London, Philadelphia, 1991. 504 pages with figures and tables, £60.00

Pathology of Reproductive Failure (Monographs in Pathology) edited by Frederick T. Kraus, Ivan Damjanov & Nathan Kaufman. Williams & Wilkins, Baltimore, 1991. 362 pages fully illustrated with plates, £52.00.

Fetal Heart Rate Monitoring. Second edition edited by Roger K. Freeman, Thomas J. Garite & Michael P. Nageotte. Williams & Wilkins, Baltimore, 1991. 230 pages fully illustrated, £33.00

Proceedings and symposiums

Gamete Interaction: Prospects for Immun contraception (Proceedings of the Third Contraceptive Research Development Program International Workshop sponsored by the World Health Organization held in Argentina in November 1989) edited by Nancy J. Alexander, David Griffin, Jeffery M. Spieler & Geoffrey M. H. Waites. Wiley-Liss, New York, Chichester, 1991, £93.50



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CONTENTS

- 749 Commentary
Progestogens, lipid metabolism and hormone replacement therapy
D. Crook & J. C. Stevenson
- 751 Fetal heart block associated with maternal anti-Ro (SS-A) antibody—current management.
A review
K. S. Oláh & H. Gee
- 756 Companionship to modify the clinical birth environment: effects on progress and perceptions of labour, and breastfeeding
G. J. Hofmeyr, V. C. Nikodem, W.-L. Wolman, B. E. Chalmers & T. Kramer
- 765 Prospective comparison of videopelviscopy with laparotomy for ectopic pregnancy
R. Baumann, A. L. Magos & A. Turnbull
- 772 Audit of workload in gynaecology: analysis of time trends from linked statistics
J. A. Ferguson, M. J. Goldacre, J. Henderson & M. D. G. Gillmer
- 778 Pretreatment of the primigravid uterine cervix with mifepristone 30 h prior to termination of pregnancy: a double blind study
M. Cohn & P. Stewart
- 783 Follicular development in spontaneous and stimulated cycles in women with minimal-mild endometriosis
T. A. Mahmood, I. E. Messinis & A. Templeton
- 789 Outcomes of referrals to gynaecology outpatient clinics for menstrual problems: an audit of general practice records
A. Coulter, J. Bradlow, M. Agass, C. Martin-Bates & A. Tulloch
- 797 'Nuns, virgins, and spinsters.' Rigoni-Stern and cervical cancer revisited
M. Griffiths
- 803 Increased plasma levels of vasoactive intestinal polypeptide in pre-eclampsia
N. Holst, P. Qian, B. Aune, T. G. Jenssen & P. G. Burhol
- 807 Reproducibility of ultrasonic measurement of fetal cardiac haemodynamics
A. R. Beeby, W. Dunlop, A. Heads & S. Hunter
- 815 Symptoms analysis for the diagnosis of genuine stress incontinence
E. Versi, L. Cardozo, D. Anand & D. Cooper
- 820 Relation of fetal blood gases and data from computer-assisted analysis of fetal heart rate patterns in small for gestation fetuses
L. S. M. Ribbert, R. J. M. Snijders, K. H. Nicolaides & G. H. A. Visser
- 824 Computerization of a colposcopy clinic
W. P. Soutter
- 829 Direct antenatal fetal electrocardiographic waveform analysis
S. Arulkumaran, U. Nicolini, N. M. Fisk, Y. Tannirandorn, K. G. Rose & C. H. Rodeck
- 832 Difficulties in the diagnosis of congenital toxoplasmosis by cordocentesis. Case report
R. E. Holliman, J. D. Johnson, G. Constantine, J. G. Bissenden, K. Nicolaides & D. Savva
- 835 Short communication
CA 125 and preterm prelabour rupture of the membranes
P. J. Danielian
- 837 Haematometra secondary to hormone replacement therapy. Case report
N. Morris, N. Amso & P. Chalk
- 839 Correspondence
- 844 Book reviews



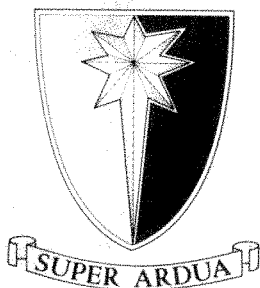
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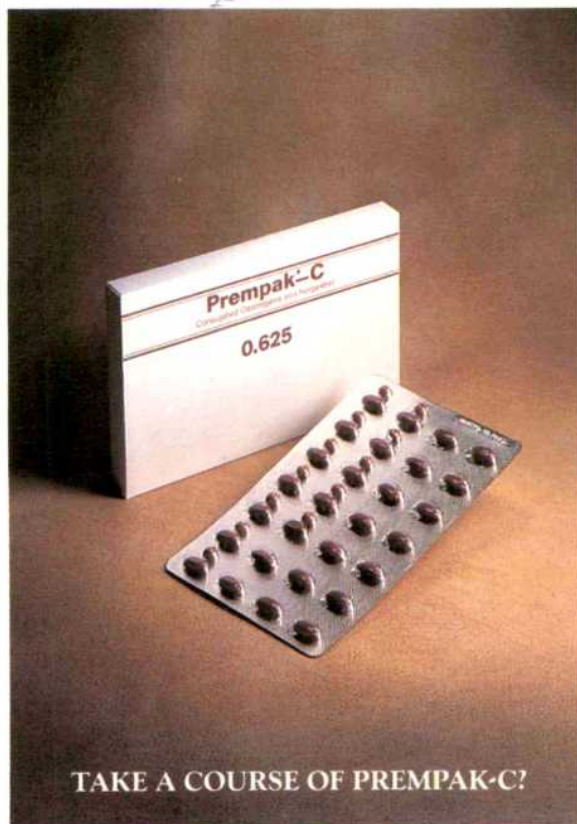
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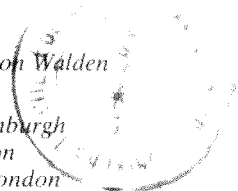
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Authors should describe clearly the design of their investigation and the source of the data. All statistical methods should be specified so that it is clear which was used where. Papers omitting this information may be returned without review. The basic principle to follow is to supply sufficient information about the design and methods of analysis to allow the research to be repeated by someone else.

The journal has published check lists to guide contributors preparing accounts of certain types of research. These appeared in 1989 (Vol 96): Bracken M. B., Reporting observational studies, 383–388; Wald N. & Cuckle H., Reporting the assessment of screening and diagnostic tests, 389–396; Grant A., Reporting controlled trials, 397–400.

Some points of detail to note are:

- (1) It is not acceptable to present the results of a statistical analysis solely by a *P* value—actual results such as means or proportions should always be given, along with the test statistic.
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Authors are referred to the general statistical guidelines of Altman *et al.* (1983) for advice about the presentation and interpretation of the statistical aspects of their research.

Altman, D. G., Gore, S. M., Gardner, M. J. & Pocock, S. J. (1983) Statistical guidelines for contributors to medical journals. *Br Med J* 286, 1489–1493.

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Manuscripts should contain a statement that the work was approved by the ethics committee of the institution in which it was done and that subjects gave informed consent to the work. The editors reserve the right to reject papers if they consider the ethical justification to be questionable.

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In the text, use the name of the author(s) followed by their date of publication; where there are two authors use the form: Smith & Brown 1972; where there are more than two authors use Robinson *et al.* 1979.

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COMMENTARIES

Stopping smoking—again

All three randomized trials of interventions to reduce smoking in pregnancy that have been published since the last Commentary in this Journal (Lumley 1987) have important features in common (Ershoff *et al.* 1989; Hjalmarson *et al.* 1991; Haddow *et al.* this issue of the Journal p. 859). All three integrated the intervention into usual antenatal care. All involved a personal introduction of the programme to the pregnant women, in two trials by obstetricians and in the third by a health educator. All included a self-help smoking cessation manual as a key component in the experimental group. All three planned to use biochemical markers to confirm self-reported smoking. Information on smoking was collected by assistants who were unaware of which group (intervention or control) the woman had been assigned to. The descriptions of the interventions themselves are detailed enough to permit the strategies to be replicated, or indeed implemented routinely, elsewhere. Thus these three trials satisfy many of the criticisms of earlier experiments (Windsor & Orleans 1986).

What contribution do they make to the continuing debate in this area of practice? The first is that they strengthen the case for emphasising *how* to give up smoking and the use of pregnancy-specific behavioural strategies. These were recommended in earlier reviews as seeming to be more effective than advice to stop (Lumley 1987; Lumley & Astbury 1989). There are four trials, summarized in Table 1, which used this approach, and their effectiveness is shown by the typical odds ratio of 0.28 [95% confidence interval 0.12–0.32]. In other words, there is a substantial and statistically confident reduction in smoking.

Both Ershoff *et al.* (1989) and Hjalmarson *et al.* (1991) provided the women in their control groups with personal advice to quit, supplemented by written material. In fact their control groups received a more powerful intervention than some experimental groups have done in the past. This was borne out by the relatively low smoking rates at 30–34 weeks in

their control groups of only 84.5% (Ershoff *et al.* 1989) and 91.4% (Hjalmarson *et al.* 1991).

Haddow *et al.* (1991) took advantage of a regional programme for maternal serum alpha-fetoprotein screening as a time and place to introduce the intervention. The other novel aspect of their approach was to combine a self-help stop-smoking booklet with personal feedback to the woman about her own blood levels of a smoking by-product (cotinine) interpreted to her in terms of the likely effect of this on birthweight. This trial took on two difficult issues. First of all it was carried out at multiple sites providing both public and private prenatal care which made the problems of maintaining staff enthusiasm and compliance over a 4-year study even greater than usual. Second, the criterion for recruitment into this trial was smoking 10 or more cigarettes a day, so it involved the heaviest smokers. Only a quarter of pregnant US smokers fall into this group (Ershoff *et al.* 1989; Haddow *et al.* 1991), therefore it is not surprising that this trial came up against a problem which has been reported before in anti-smoking studies, namely poor implementation. The proportion of women who returned for the repeat cotinine sampling was unacceptably low. As this second sample was to be the measure of change in smoking behaviour it was not possible to assess the effectiveness of the combined approaches.

There are some reasons to be doubtful about the specific feedback provided here. Feedback which consisted of showing pregnant women their carbon monoxide levels had no effect on smoking behaviour in an earlier trial (Bauman *et al.* 1983). Feedback has been successful in pregnancy when it involved demonstration of fetal activity, though neither study followed participants for more than a few weeks (Kelly & O'Connor 1984; Reading *et al.* 1984). Although the feedback in the current trial did have a fetal reference, reduction in birthweight, it is far from certain that this would be persuasive. Low birthweight is not necessarily seen as undesirable (Rajan & Oakley 1990). Smaller babies may even be seen as advantageous, so much so that

Table 1. Effect of anti-smoking interventions on continued smoking during pregnancy

Intervention study	Intervention	Control	Odds ratio (95% CI)
Advice			
Baric <i>et al.</i> (1976)	54/63	45/47	0.33 (0.09–1.16)
Burling (unpublished)	62/69	68/70	0.33 (0.08–1.16)
MacArthur <i>et al.</i> (1987)	483/493	483/489	0.67 (0.24–1.86)
Lilley & Forster (1986)	73/77	72/73	0.31 (0.05–1.82)
Typical odds ratio (95% CI)			0.42 (0.22–0.80)
Feedback			
Bauman <i>et al.</i> (1983)	36/36	43/43	1.00 —
Reading <i>et al.</i> (1984)	20/39	20/26	0.34 (0.13–0.95)
Typical odds ratio (95% CI)			0.34 (0.13–0.95)
Behavioural strategies			
Windsor <i>et al.</i> (1985)	88/102	102/104	0.19 (0.07–0.54)
Sexton & Hebel (1984)	22/326	36/328	0.14 (0.10–0.21)
Ershoff <i>et al.</i> (1989)*	93/126	98/116	0.53 (0.29–0.98)
Hjalmarson <i>et al.</i> (1991)*	388/444	191/209	0.61 (0.36–1.03)
Typical odds ratio (95% CI)			0.28 (0.18–0.32)

Table adapted from Lumley & Astbury (1989)

*Smoking at 30–34 weeks gestation

one very successful smoking reduction trial confronted the myth about small babies and easy labours as an intrinsic component of the information provided to participants (Sexton & Hebel 1984).

The offer of free stop-smoking groups was once again shown to have a very poor response (Ershoff *et al.* 1989).

The second contribution of these trials is that two of them provide information on birthweight and gestation at delivery among participants and one includes data on fetal and infant deaths as well. Hjalmarson *et al.* (1991) found a birthweight difference of 71 g in favour of the experimental group and Haddow *et al.* (1991) found an overall difference of 31 g, which was twice as large (66 g) when the analysis was restricted to the top 50% of the participating centres when ranked in terms of the proportion of women who returned for repeat cotinine sampling. None of these differences was statistically significant. Four trials have now shown modest gains in birthweight (Hjalmarson *et al.* 1991; Haddow *et al.* 1991; Sexton & Hebel 1984; MacArthur *et al.* 1987). The reasons for the discrepant findings in Donovan's (1977) study of no change in birthweight despite a significant reduction in self-reported smoking now seem even more likely to lie in the unreliability of the smoking information and the probability that socially desirable responses were given to the interviewer.

A more detailed analysis by MacArthur & Knox (1989) of data from their smoking reduction trial showed that the difference in birthweight between those who gave up smoking at any time before 16 weeks and the persistent smokers was 160–170 g, after adjustment for maternal age, height, primiparity, gestation at delivery and the infant's sex. Stopping after 16 weeks was associated with a statistically significant but smaller difference (75 g).

The unresolved questions are whether the gain in birthweight is of clinical significance, whether there is any change in every preterm delivery with a reduction in smoking and whether there is a reduction in perinatal mortality. A brief calculation from the data in Table 1 of the actual numbers of women who gave up smoking in even the most successful trial—105—shows that no study has been powerful enough to begin to answer any of these key questions.

What we need now are trials using the most effective intervention which is at the same time inexpensive enough to have widespread applicability. The total cost of the programme described by Ershoff *et al.* (1989) was \$11 per participant in 1985–87 which compares well with the costs of some current antenatal investigations of unproven benefit. Such trials need to be large enough to address the substantive unresolved questions and that means *very* large indeed. Sufficient information is available from the published trials

to make a reasonable estimate of the required sample size.

Meanwhile, obstetricians and midwives should ensure that material is accessible to all pregnant women in their care which will help them to stop smoking (Petitti *et al.* 1991). At the same time, in the interests of healthy mothers and babies, obstetricians and midwives should continue to support the population strategies towards a progressive reduction in cigarette smoking in the whole of society: to increase cigarette excise taxes; to ban all forms of tobacco advertising; to challenge legally whether tobacco manufacturers are responsible for health outcomes; to enforce the laws which prohibit sales to children and adolescents; to make public areas non-smoking and to develop smoking policies for institutions and workplaces.

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First trimester prenatal diagnosis: chorion villus sampling or amniocentesis?

The history of prenatal diagnosis of fetal abnormality and genetic disease has been short but explosive. There continue to be new advances and challenges. Now the drive is

towards increasing first trimester diagnosis. Positive diagnosis may be helpful in a number of ways and allows several options of which termination of pregnancy is but one (Neilson & Grant

1989). Abortion is often preferred if the baby has a major handicapping abnormality, including chromosomal abnormality (Drugan *et al.* 1990), or a serious inherited disease, or a lethal malformation. Although the decision to abort a wanted pregnancy because of fetal abnormality is profoundly upsetting whatever the gestational age, there is merit in earlier termination. Firstly, early suction aspiration is a simpler, kinder and probably safer procedure than second trimester termination by either prostaglandin stimulation or, less commonly, dilatation and evacuation. Secondly, first trimester termination of pregnancy occurs at a time when the pregnant status of the woman is not obvious to others, so the decision to abort is more private. Thirdly, the fetus is smaller and less developed, and the mother has not yet perceived its movements; its destruction is perhaps less poignant. For all these reasons, first trimester investigation, if proved to be safe and reliable, is valuable so that both diagnosis and (if appropriate) termination of pregnancy may be completed before the start of the second trimester.

The thrust towards early diagnosis has taken place through four techniques—ultrasound, maternal biochemical screening, chorion villus sampling (CVS), and amniocentesis.

The constantly improving imaging capabilities of ultrasound equipment have allowed more detail of fetal anatomy to be seen in the first trimester by transabdominal (Green & Hobbins 1988) and, more especially, by transvaginal ultrasound (Rottem *et al.* 1989). Because the transvaginal probe is held close to the uterus, without intervening layers of fat and muscle, higher ultrasound frequencies can be used to improve resolution and a number of positive prenatal diagnoses have been made. Two words of caution are appropriate. First, with each quantum leap in imaging, new structures are seen and it can take some time before their significance is fully understood. Second, the technique of abortion (vacuum aspiration) makes anatomical confirmation of the ultrasound diagnosis by the pathologist difficult (Editorial 1989). There may be conditions such as skeletal dysplasias, in which the need for accurate pathological diagnosis to allow future counselling overrides the advantages of suction termination of pregnancy.

The demonstration of structural abnormality during the first trimester often indicates a need for further investigation rather than leading

inevitably to termination of the pregnancy. As in the later trimesters, the major significance of certain dysmorphic features is their association with other abnormalities, especially chromosomal abnormalities. Additional cytogenetic or biochemical testing may therefore be necessary.

There is another way of identifying high risk pregnancies that would not previously have been seen as at increased risk of karyotypic abnormality by traditional criteria based on maternal age and past reproductive history. This is by maternal serum biochemical screening, notably of alphafetoprotein (AFP), human chorionic gonadotrophin (hCG), and oestriol. The role of maternal biochemical screening and its influence on first trimester diagnosis is complex. It has been argued by some that invasive diagnostic procedures for cytogenetic analysis should only be undertaken when the biochemical/maternal age risk exceeds 1 in 280. This would allow many older pregnant women to avoid the risks of invasive testing. However, second trimester serum screening detects only about 70% of fetuses with Down's syndrome and, unfortunately, first trimester testing even less sensitive and specific (Brock *et al.* 1990; Nebiolo *et al.* 1990). To deny high risk women first trimester diagnosis when they are very anxious or would not accept a late termination of pregnancy seems harsh when the procedures have been widely advocated and older women have been encouraged to come forward for early testing.

CVS has been rapidly assimilated into prenatal diagnosis. Its safety and efficacy have been compared with conventional late genetic amniocentesis in large randomized trials in Canada and Europe. Both trials have now been reported (Canadian Collaborative CVS—Amniocentesis Clinical Trial Group 1989; MRC Working Party on the Evaluation of Chorion Villus Sampling 1991). Although CVS has the advantage of early performance and relatively rapid analysis, there are disadvantages. First, CVS is less safe—this is not surprising as it is a much more traumatic procedure than amniocentesis. Adding to the risk of miscarriage have been recent anxieties about a possible association with fetal limb defects when CVS has been performed at less than 10 weeks (Firth *et al.* 1991). The European MRC study has thrown no further light on this. Second, there is the problem of confined placental mosaicism which is found eight times more commonly at CVS than at second trimester amniocentesis. Such cytogenetic differences between placenta

and fetus have caused diagnostic confusion, some inappropriate terminations of pregnancy, and even the failure to recognise a major chromosomal abnormality of the fetus (Gosden 1991).

The problems associated with CVS have led to the investigation of early (i.e., first trimester) amniocentesis. Possible advantages include greater safety, less likelihood of confusing reports because of confined placental mosaicism, and the inclusion of biochemical as well as cytogenetic analysis. In addition, culture and harvesting of amniotic fluid cells is less labour intensive in the laboratory than the processing of chorionic villi. It is therefore less expensive. Since, however, more than 70% of cells in amniotic fluid up to 15 weeks are derived not from the fetus but from the membranes and trophoblast, there is a substantial possibility that confined placental abnormalities may be much more of a problem with first trimester than second trimester amniocentesis. Traditionally genetic amniocentesis has been performed at 16 weeks gestation because of reportedly less successful culture rates at lower gestation. With better modern culture techniques, including hormonally supplemented medium and special culture vessels, successful testing is possible earlier and reports should be available from efficient cytogenetic laboratories in 1–2 weeks (Romero *et al.* 1991). The Belfast group have reported 222 consecutive amniocenteses performed before 14 weeks (Nevin *et al.* 1990). Amniocentesis was successfully accomplished in all cases, as was cytogenetic analysis (complete in a mean time of 10 days) with total subsequent abortion rate of only 1.4%. Other groups have not been so successful with cultures (e.g., Rooney *et al.* 1989) but have confirmed the technical feasibility and apparent safety of the procedure.

Biochemical studies of fluid obtained by first trimester amniocentesis have produced conflicting results. Amniotic fluid acetylcholinesterase estimation has been associated with both false positive (Burton *et al.* 1989) and false negative (Evans *et al.* 1989) results. There is little information about the value of amniotic fluid AFP for the first trimester diagnosis of fetal neural tube defects. In this issue of the Journal (p. 866), Wathen and colleagues highlight a potential source of confusion. Early amniocentesis differs from second trimester amniocentesis because there are two sacs during the first trimester—the

amniotic cavity and the extra embryonic coelom. The amnion, which separates the two compartments, can be seen clearly on transvaginal scanning. Fluid obtained from these two sources differ in their concentration of both hCG (Wathen *et al.* 1991a) and AFP (Wathen *et al.* 1991b). If AFP levels are found to be important for the diagnosis of neural tube defects during the first trimester, it will be important to know what type of fluid has been sampled. This may also explain apparent inconsistencies in the usefulness of acetylcholinesterase, but it is unlikely to carry any implications for cytogenetic analysis.

Very little is yet known of the relative safety, accuracy, costs and failure rates of first trimester amniocentesis. There are, as we have tried to demonstrate, theoretical advantages and disadvantages to encouraging its wider use. It is quite obvious to us that a large multicentre randomized controlled trial is now required to compare first trimester amniocentesis and CVS. This must include not only assessment of short term safety and accuracy but also long term follow up to identify any complications in children born after these sampling methods have been used. Limb deformities and impaired respiratory function should receive particular attention as possible sequelae of CVS and early amniocentesis, respectively.

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Some historical aspects of toxæmia of pregnancy.

A review

IRVINE LOUDON

If the cause of a disease is unknown, renaming it reflects new theories and produces a comforting illusion of progress. Toxaemia is a prime example. Since the 18th century it has appeared under such headings as puerperal convulsions, puerperal nephritis and albuminuria, puerperal albuminuria and convulsions, eclampsia, toxæmia and pre-eclampsia (or pre-eclampsia) and recently as pregnancy associated hypertension or hypertensive disease in (or, of) pregnancy. For historical reasons I will use 'toxæmia' throughout his paper.

In the early years of the 19th century when only the end stage of toxæmia, eclampsia, was recognised, it was generally believed to be a special form of epilepsy ('convulsio') associated with pregnancy. A spate of new theories followed the discovery by Rayer in France in 1839 and John Lever in London (Lever 1843) that eclampsia was associated with albuminuria. Lever also made the important observation that pregnant women with oedema, blurred vision, and headaches, had albumen in their urine, confirming his suspicion that these symptoms were part of the same disorder and warning signs of impending eclampsia. (The measurement of blood pressure as a regular clinical procedure did not begin until around 1910). Lever also demonstrated that eclampsia was more common in first pregnancies than subsequent ones.

Bright's description of acute nephritis in 1827 made kidney diseases fashionable. Since oedema and albuminuria were characteristic features of both eclampsia and nephritis, eclampsia was thought to be a renal disorder and the convulsions were attributed to uraemia. When this was disproved, new theories proliferated. Some said that eclampsia was due to com-

pression of the ureters, others to a summation of external irritants. A few returned to the idea that it was simply epilepsy. In 1884, Delore was certain the cause was a specific bacterium which he named *Bacillus eclampsiae* until, to his dismay, it was identified as the common organism *Proteus vulgaris*. Then the idea took hold that the disorder was due to the existence of specific toxins of pregnancy, which were produced in the placenta according to Ahlfeld in 1894 (DeLee 1905), and thus it came to be called toxæmia.

In 1905 J. B. DeLee of Chicago read everything on toxæmia he could lay his hands on, and concluded with a touch of exasperation:

'You all know the trite expression of Zweifel, that eclampsia is the disease of theories. That I have had more and more proved to me as I waded through the oceans of literature . . . As a matter of fact we know practically nothing of the causation of eclampsia. A theory has only to be set up by one investigator to be knocked down by another . . . only one point seems to be generally conceded, that eclampsia is due to the action of a toxin in the blood upon the nerve centers'. (DeLee 1905).

Treatment and prevention

When the cause of a disease is obscure, rational treatment is difficult and there is often a multiplicity of remedies. So it was with toxæmia. Medical remedies have included (in roughly chronological order) bleeding and purging, bed-rest, heavy sedation with morphine, chloral, chloroform etc, veratrum viride, the Stroganoff regimen, magnesium sulphate, intravenous dextrose, rectal tribromoethanol, hydralazine, diuretics, benzodiazepines and oral antihypertensive agents.

It was well known, however, that delivery of the baby cured toxæmia. Induction of labour

was therefore the surgical standby. Unfortunately the methods of induction before the 1930s, which ranged from rupture of membranes to the insertion into the cervix of bougies or laminaria tents, were both uncertain and risky—features which prompted certain obstetricians in the USA during the early years of this century to resort to caesarean section. The results were discussed by an obstetrician in Chicago (Holmes 1921) in a memorable paper, *'The fads and fancies of obstetrics'*. He showed that in the 19th century the maternal and fetal mortality rates for eclampsia were 20.4% and 33.3% respectively. 'Modern [medical] methods exhibited mortalities of 19% and 39.6%, while in caesarean section . . . the deaths were 34.8% and 25.9% respectively'. In short, caesarean section saved a few babies at the cost of killing more mothers. As a treatment for toxæmia of pregnancy, caesarean section was 'clearly and definitely indefensible'. Attention was therefore directed away from treatment to prevention.

By the early 1920s, when the high and undiminishing level of maternal mortality had become a scandal throughout the Western world (Loudon 1988), antenatal (prenatal) care came to be seen as the panacea. Prevention was the watchword and it was fashionable to speak of obstetrics as a branch of preventive medicine. In Britain, and even in the USA where government 'interference' in obstetric practice was anathema, antenatal clinics, some charitable, some supported by government funds, sprang up like mushrooms. However, for antenatal care to be effective in the prevention of maternal and fetal deaths from toxæmia, certain conditions need to be fulfilled. The public and the profession must be persuaded of the importance of regular antenatal care and early booking. In private practice as well as clinics, the minimum procedures of blood pressure measurement and urinalysis must be done and recorded. If signs of toxæmia develop, there must be universal procedures (without financial hindrance) for rapid referral to specialist care. Finally, the specialists must be competent to deal effectively with toxæmia. Because it was rare for all these conditions to be met, antenatal care at the national level was a failure until the 1940s at the earliest. Maternal mortality in Britain, far from declining, rose steadily to reach the highest 20th century level in 1934, in spite of the multitude of antenatal clinics and continual exhortations concerning antenatal care.

Incidence and mortality

Some of the most interesting historical questions are those concerning the incidence and mortality of toxæmia in different countries in the past. Sadly, there are few estimates of incidence and most are concerned solely with eclampsia. In a series of unselected home confinements between 1834 and 1843, Lever (1843) found an incidence of 190/100 000 deliveries with a mortality rate of just over 25%. In 1926, a doctor in Minnesota collected data on midwifery from 26 rural practitioners and found an unusually high incidence of 540/100 000 confinements (Piper 1926). Reports from individual practitioners in the USA usually reported a lower incidence level, but as they were based on small numbers, they show wide variations and do not inspire great confidence. For example, J. C. Bliss of New York had four cases of eclampsia in 815 deliveries giving a rate of 490/100 000 (Bliss 1847), E. P. Bernardy of Philadelphia reported eight cases in 1387 deliveries, giving a rate of 576/100 000 (Bernardy, 1892). W. De Wees of Kansas reported 1000 deliveries and two puerperal convulsions, giving a rate of 200/100 000 (De Wees 1888). William Dunn of Boston mentioned three cases of puerperal convulsions in 1168 deliveries giving a rate of 257/100 000 (Dunn 1891). There are many case reports from hospitals, but they are of little value because they were so often selected and unrepresentative series.

We are on much firmer ground when it comes to mortality, although initially there was a snag. Following Lever's discovery of albuminuria in eclampsia, the General Register Office made an uncharacteristically silly decision to separate deaths from eclampsia and pre-eclamptic toxæmia, burying the latter in a dustbin-category called 'other diseases of the kidney' from which they cannot be recovered. It was not until the adoption of the ICD (the first revision) in England and Wales in 1911 that pre-eclamptic and eclamptic deaths were brought together, revealing that about 85%–90% of toxæmic deaths were in fact due to eclampsia. What, then, were the mortality rates and how did they vary?

Throughout the Western world from the earliest reliable records to the mid-1930s, maternal mortality was dominated by the well-known triad of sepsis (puerperal fever), toxæmia, and haemorrhage (ante- and post-partum). If deaths from abortion are excluded, in round figures between 30% and 45% of maternal deaths were

Table 1. The total maternal mortality rates and the rates for toxæmia for various countries up to the mid-1930s, and mortality rates for toxæmia as a percentage of total maternal mortality. The definition of the category of deaths attributed to toxæmia, albuminuria and convulsions and so on, is also shown for each country (in parenthesis)

Country and date (definition)	Maternal mortality (rate/100 000 births)		Toxæmia (as a percentage of total)
	Total	Toxæmia	
England and Wales, 1872-76 (Puerperal convulsions)	542	63	11.6%
England and Wales, 1933 (Puerperal albuminuria and convulsions = 83.5%; toxæmia of pregnancy = 16.5%)	451	76	16.9%
England and Wales, 1930-32—Married women only			
All social classes	413	79	19.1%
Social classes I and II	444	81	18.9%
Social class III	411	81	19.7%
Social class IV	416	85	20.4%
Social class V	389	68	17.4%
(Definition as for England and Wales 1933)			
Wales 1929-33 (All toxæmias)	541	141	26.0%
Scotland (Puerperal convulsions and albuminuria)	613	85	13.8%
Eire (Albuminuria and convulsions)	482	53	11.1%
Switzerland, 1922 (Toxæmia of pregnancy)	534	66	12.3%
The Netherlands, 1933 (Albuminuria and eclampsia)	314	42	13.3%
Sweden, 1931-35 (Eclampsia)	345	c.50	14.5%
United States—Death registration area 1921 (Puerperal albuminuria and convulsions)	682	182	26.7%
Kentucky, USA, 1932-36 (Toxæmia)	500	65	13%
South Carolina, USA, 1934-35			
White population	662	284	43.0%
Black population	1034	374	36.2%
(Albuminuria and eclampsia)			

Sources used in the Table:

England and Wales: *Annual Reports of the Registrar General for England and Wales* (Various years), Ministry of Health (1937). Wales: Ministry of Health (1937) *Report on Maternal Mortality in Wales*. Scotland: Mackinlay P. L. (1947). Eire: *Annual Reports of the Registrar General for Ireland*. (Various years). The Netherlands: *Statistiek van de sterfte naar den leeftijd en de oorzaken van den dood* (Various years). Switzerland: League of Nations, Health Organization. (1928). Sweden: Hogberg U. (1985). USA 1921: Woodbury R. M. (1926). Kentucky, USA: Crittenden C. B. & Skaggs L. (1940). South Carolina, USA: South Carolina Medical Association, Committee on maternal welfare. (1936 and 1941).

Table 2. Maternal mortality rates in the USA, England and Wales, and the Netherlands from 1920 to 1960. Rates expressed as maternal deaths per 100 000 live births

Year	USA	England & Wales	The Netherlands
1920	689	433	240
1930	636	440	333
1940	376	261	235
1950	83	87	105
1960	37	39	37

Source: The published vital statistics of the three countries.

due to sepsis, about 20% to toxæmia, and about 15% to haemorrhage. What is remarkable is the constancy of these proportions in different countries and different periods, regardless of widely different levels of total maternal mortality (Loudon 1988). Having said that, however, where international differences did occur, they were usually greatest in deaths from toxæmia. Table 1 gives some examples. Can we discern any informative differences?

In most Western countries during the early decades of this century, deaths due to toxæmia/eclampsia ranged from about 50 to 150 per 100 000 live births, with a mean of around 70. In Britain from 1912 to the mid-1930s, mortality

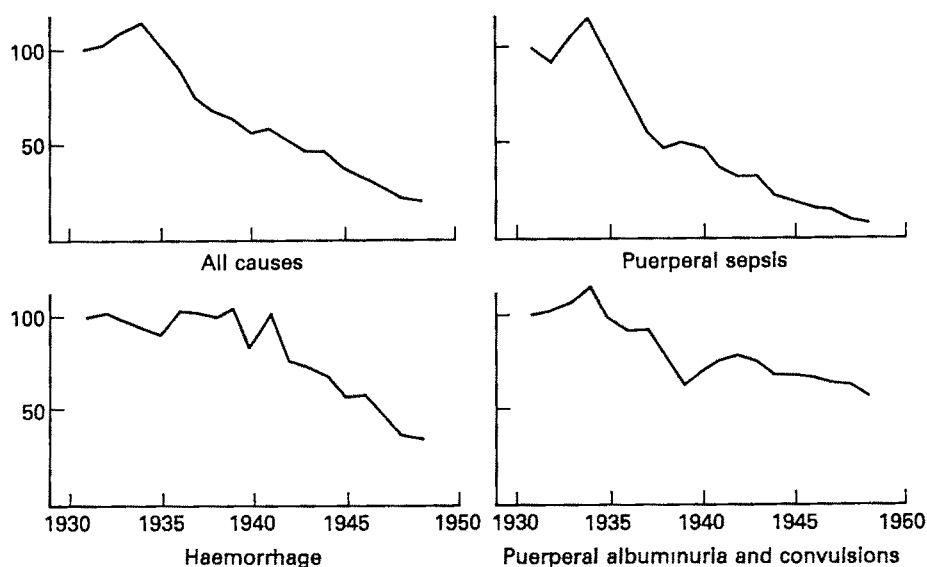


Fig. 1. England and Wales, 1930–1949. The trend in mortality from various causes indexed to 1930 = 100.

from toxæmia was consistently highest in Scotland, lowest in Ireland, and midway in England and Wales. I am unable to explain this pattern. In England and Wales the lowest mortality from toxæmia occurred in social class V and the highest in social class IV (Table 1), but in general there is no evidence of a social class gradient in deaths from toxæmia. The Netherlands scored the lowest rate (42) and the USA the highest (182). On the whole—and there are certainly exceptions—countries or regions with exceptionally high or low mortalities from all causes tended to show correspondingly high or low *pro-*

portional rates of deaths due to toxæmia. We can see this, for example, in the rates for the Netherlands and Sweden on the one hand and the USA and South Carolina on the other in Table 1. It is interesting that a report in 1932 suggested the *incidence* of 'pregnancy toxæmia' in the Netherlands was unusually high, occurring in at least 25% of pregnancies as revealed by hypertension with or without albuminuria, while the mortality was unusually low; but the incidence rate referred to hospital cases. The authors of the report attributed this to 'stricter ante-natal supervision and early hospitalization

Table 3. England and Wales. The maternal mortality rate for all direct maternal deaths excluding abortion for various quinquennial periods from 1925–30 to 1971–75, together with deaths from toxæmia (hypertensive disease in pregnancy), post-partum sepsis, haemorrhage (ante- and post-partum) and other causes, shown in each case as rates per 100 000 live births and as percentages of total maternal mortality

Year	Total maternal deaths	Toxæmia	Sepsis	Haemorrhage	All other causes
	Rate (%)	Rate (%)	Rate (%)	Rate (%)	Rate (%)
1926–30	371 (100)	79 (21)	137 (37)	50 (13)	105 (28)
1931–35	367 (100)	66 (18)	134 (36)	46 (13)	121 (33)
1941–45	182 (100)	53 (29)	18 (10)	40 (22)	71 (39)
1951–55	56 (100)	17 (30)	2 (4)	11 (20)	26 (46)
1961–65	23 (100)	5 (22)	1 (4)	4 (17)	13 (57)
1971–75	12 (100)	3 (25)	<1 (<4)	2 (16)	6 (50)

Source: *Annual Reports of the Registrar General*. (Various years) Macfarlane A. & Mugford M (1986) Table A, 10.2.

of such cases' in the Netherlands compared with England (Ministry of Health 1932).

In so far as any country succeeded in reducing mortality from toxæmia, it was probably through early referral and induction of labour, and the Netherlands may indeed have been successful in this respect during the inter-war period. Conversely, the high levels in the 'Deep South' of the USA may reflect the poor standard of maternal care which was an undoubted feature of these states (Loudon 1988). In passing, it is worth noting that black mothers in the USA always suffered a higher absolute rate of toxæmic deaths, but usually a lower rate when expressed as a percentage of all maternal deaths. With international comparisons of toxæmia there are often problems of differing definitions; apart from this, however, I have found it difficult to find plausible explanations for the different rates of mortality from toxæmia.

From the mid-1930s, however, some very interesting features emerge. For maternal mortality as a whole there were first the steep, sustained and continuous fall, and secondly the extraordinary convergence by 1960 of maternal mortality rates in different countries which had been miles apart in the 1920s and 1930s. This can be seen in Table 2. The early years of the decline are particularly instructive. Figure 1, for instance, shows cause-specific trends from 1930 to 1949, indexed to 100 in 1930. The steepest fall occurred in deaths due to post-partum sepsis, and was due initially to the introduction of the sulphonamides (Loudon 1987). Deaths from haemorrhage remained more or less level until the mid-1940s. The subsequent decline in this category can be attributed to two factors. First, Chassar Moir's work on ergometrine. This came into general use in the 1940s, and its widespread employment, especially with the technique of intravenous ergometrine with the delivery of the anterior shoulder, greatly reduced the incidence and mortality due to post-partum haemorrhage (Chassar Moir 1956). Second, blood transfusion became widely available to the civilian population as a result of wartime measures. Finally, there were the deaths from toxæmia. Throughout the Western world they declined more slowly than deaths from any other puerperal cause.

Now look at Table 3, because it shows how the extremely rapid fall in deaths due to sepsis pushed deaths due to toxæmia from second to first place in the list of causes. From 1940, while deaths from sepsis formed a rapidly decreasing

proportion of total mortality, toxæmic deaths moved up from 18% of total mortality in 1931–1935 to 30% in 1951–55. Although the decline in the mortality rate from toxæmia (a decline from 66 in 1931–35 to 3 in 1971–75) is impressive, toxæmia came to be the most important and intractable part of maternal mortality in the second half of the 20th century.

In her review of deaths due to hypertensive disease in pregnancy in developing countries (L. Duley personal communication) has emphasized the continuing 'holocaust' of maternal deaths. Is there a similarity between the experience of maternal mortality in Western countries in the past and that in developing countries today? To some extent there may be. In some parts of Africa and the Far East it looks as if the overall rate of maternal mortality and the distribution by cause resembles the position in the West in the 1920s. In other countries, parts of South America for example, the present position may lie closer to the British situation in the 1940s and 1950s. At the risk of patronizing overtones, it is very tempting to suggest that all countries will ultimately follow the same path, with the West leading and the developing countries lagging behind by a few decades. If that proves to be the case it will be a rare example of the trite phrase that 'history has lessons for the present'. It is certainly possible, however, that such a simplistic assumption will be proved wrong; but even if it is I suspect that everywhere, deaths from toxæmia/hypertensive disease will prove the hardest nut to crack.

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Cotinine-assisted intervention in pregnancy to reduce smoking and low birthweight delivery

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Abstract

Objective—To investigate the feasibility and impact of integrating a cotinine-assisted smoking intervention programme with an existing antenatal maternal serum alpha-fetoprotein (AFP) screening service for open neural tube defects.

Design—A multisite randomized controlled trial.

Setting—139 physician offices and clinic sites in Maine providing antenatal care.

Subjects—2848 pregnant women who smoked 10 or more cigarettes daily, enrolled at between 15 and 20 weeks gestation, from a population base of approximately 18 000 pregnancies.

Interventions—The women were individually allocated at random to intervention or control groups within each centre at the time the serum sample was received for AFP measurement. The intervention group received an interpreted measurement of the serum cotinine, reported through the physician to the woman, along with a self-help smoking cessation booklet and a repeat serum cotinine measurement one month later, again interpreted and reported through the physician to the woman. Women in the control group received the usual anti-smoking advice provided by the antenatal care site and were not told of the study.

Main outcome measures—Birthweight, physician cooperation with study protocol (as measured by effectiveness in obtaining repeat serum samples for cotinine measurements).

Results—Pregnancy outcome data were available for 97% of the study population, including birthweight for 2700 singleton viable pregnancies. The smoking intervention programme led to a significant 66 g increase in mean birthweight ($P = 0.03$; 95% CI +9 to +123 g) and to a 30% reduction in the rate of low birthweight in pregnancies managed by the 70 physicians who secured the highest rate of obtaining repeat serum samples for cotinine measurements in their intervention group. Among the remaining 69 physicians, intervention had no detectable effect on birthweight.

Conclusion—A cotinine-assisted smoking intervention programme managed from a central location as an adjunct to a maternal serum AFP screening service can, with the cooperation of physicians responsible for antenatal care, lead to a significant and cost-effective reduction in the number of low birthweight babies. This programme is inexpensive, requires little extra effort, and does not need specially trained personnel.

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Infants born to mothers who smoke during pregnancy weigh approximately 200 g less, on average, than those born to mothers who do not smoke, and the risk of being born weighing <2500 g is more than doubled (US Department of Health and Human Services 1980). The relation between cigarette smoke exposure and low birthweight is dose-dependent, as measured either by self-reported numbers of cigarettes smoked per day or by biochemical measures, such as serum cotinine (US Department of Health and Human Services 1980, Haddow *et al.* 1987), and a single serum cotinine measurement during the second trimester of pregnancy is more closely associated with birthweight than reported numbers of cigarettes smoked (Haddow *et al.* 1987). A recent randomized trial in a large metropolitan area, aimed at encouraging pregnant women to give up smoking, demonstrated that higher birthweights can be achieved if a pregnant woman reduces or stops smoking, even as late as in the second trimester (Sexton & Hebel 1984). That study employed staff trained in smoking cessation techniques who gave each study subject intensive attention in person, by telephone, and by letter. Our aim was to determine whether a statewide maternal serum alpha-fetoprotein (AFP) screening service (Haddow *et al.* 1983) for open neural tube defects could be used to achieve similar benefits on a wide scale, without specially trained personnel to counsel women and without extra local resources. We therefore decided to conduct a randomized trial in which the key element in the intervention was the use of two serum cotinine measurements; one initial measurement to help make the hazards of smoking in pregnancy personally relevant, and a second measurement a month later to provide feedback and reinforcement to the patient. The endpoint of the study was a comparison of birthweight between the intervention and control arms of the trial.

Subjects and methods

Physicians providing antenatal care throughout Maine who participated in a maternal serum AFP screening service for neural tube defects were approached individually early in 1984 and asked if they would agree to take part in a randomized trial of smoking intervention. Physicians were asked to agree to serum cotinine measurements being performed using the AFP sample for women who smoked 10 or more ciga-

rettes per day and to allow these women to be allocated at random to an intervention arm and a control arm. Explicit consent was not sought from the women themselves. The cigarette consumption was entered on the maternal serum AFP order form, and if the woman was eligible, the computer assigned her to either intervention or control group by reference to a file of random numbers. Women in the control arm of the trial received whatever standard anti-smoking advice was provided at the site where they received care, while women in the intervention arm received both the standard advice and the cotinine-assisted intervention. The trial was restricted to women who smoked 10 or more cigarettes per day, because it was more likely that giving up smoking would show a greater reduction in low birthweight than if all smokers were included, and because such women might find giving up smoking more difficult. Also, physicians participating in the study were more likely to treat the matter more seriously.

Women allocated to the intervention group had a cotinine measurement performed on the serum sample within several days after its arrival at the study centre. Two copies of a report of that cotinine measurement, which included an interpretation of its meaning, were returned to the physician. The report of the serum cotinine measurement contained a quantitative measurement of the cotinine level, with a visual display, categorizing the women into five cotinine categories. A brief text accompanied the measurement, describing the estimated effect of smoking on birthweight in relation to the woman's cotinine level, and encouraging her to stop smoking. The physician was asked to explain the report to the woman and provide her with a copy. A ten page smoking cessation booklet was provided for the physician to give to the woman with the cotinine report. This booklet provided guidance for stepwise smoking cessation based on widely used techniques, but was written in the context of pregnancy and the availability of cotinine measurements. A second serum cotinine measurement was obtained one month later, in conjunction with a regularly scheduled visit, and two copies of the individualized report were sent back to the physician, again to be shared with the woman. This second report was designed similarly to the first, but included a comparison of the first and second cotinine measurements. The text commented on the extent of change and provided further encouragement.

Table 1. Enrolment of women into the trial according to the time of randomization

Time of randomization*	Number of pregnancies screened by MSAFP†	Per cent of screened pregnancies from enrolled physicians	Per cent smoking >10 cigarettes/day‡	Numbers of cases/controls randomized§
1984	3151	56	17	157/154
1985	7572	65	17	406/402
1986	8739	72	16	486/508
1987	6166	75	17	374/361
Total	25 628	69	17	1423/1425

* Enrolment was between 1 July 1984 and 30 August 1987.

† MSAFP = maternal serum alpha-fetoprotein (total annual births in Maine are approximately 16 500).

‡ 97% of the women answered the smoking question on the MSAFP order form

§ Lost to follow-up 41/39.

The women in the control group received standard medical care, and their serum samples were frozen for cotinine measurements after completion of the pregnancies. Birthweights were obtained from the state's vital records and, where necessary, from inquiries to individual physicians who provided antenatal care. The birthweights from singleton livebirths in the two groups were then compared using a pooled, two-tailed Student's *t*-test, and the rates of low birthweight (≤ 2500 g) were compared using the χ^2 -test. Twin gestations were excluded from the analysis, because their inclusion would add an extraneous source of random error with too few to examine the effect of stopping smoking on twin pregnancies, separately. For the same reasons, the fetal deaths were excluded. Cotinine measurements were performed by radioimmunoassay (Knight *et al.* 1985). The assay

measures cotinine over the range of 5–800 ng/ml. A level of cotinine of 10 ng/ml is used as the demarcation point for distinguishing smokers from non-smokers (Benowitz *et al.* 1983).

Results

Table 1 summarizes the extent of participation according to the physician office and clinic sites in Maine during the 38 month study enrolment period, along with the numbers of cases and controls enrolled. During the enrolment period there was an increase in the number of women having maternal serum AFP screening and in the number of physicians who took part in the randomized trial. The smoking question on the AFP order form was answered by 97% of the women, and 17% of those women smoked ≥ 10 cigarettes daily. Overall, 2848 women smoking ≥ 10 cigarettes per day (1423 cases and 1425 controls) were enrolled from a population base of approximately 18 000 pregnancies cared for at 139 participating sites. Approximately 3% of the enrolled pregnancies were lost to follow-up, and just over 2% were either multiple gestations [13 (0.9%) and 8 (0.6%) in the intervention and control groups respectively] or fetal deaths [26 (1.8%) and 21 (1.5%) in the intervention and control groups respectively]. Table 2 shows that the two randomization groups were similar at entry into the trial. Women in the intervention group smoked, on average, 16.1 cigarettes daily, and had, on average, a serum cotinine level of 169 ng/ml. The control group smoked an average of 16.3 cigarettes daily, and the average serum cotinine level was 168 ng/ml.

Table 2. Selected descriptive variables in the intervention and control groups at entry to the trial

Variable	Intervention mean (SD)	Control mean (SD)
Maternal age (years)	24.2 (4.6)	24.3 (4.8)
Maternal weight (kg)	66.1 (13.6)	65.2 (13.6)
Maternal height (cm)	16.3 (6.6)	16.3 (6.8)
Gravidity	2.3 (1.3)	2.3 (1.3)
Maternal education (years)	11.9 (1.8)	11.8 (1.7)
Gestational age at enrolment (weeks)	17.7 (1.6)	17.7 (1.6)
Daily cigarette consumption	16.1 (6.5)	16.3 (6.4)
Serum cotinine level (ng/ml)	169 (89)	168 (93)

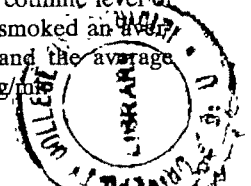


Table 3. Effect of cotinine-assisted intervention on birthweight, gestational duration and fetal and neonatal deaths for singleton pregnancies in women smoking ≥ 10 cigarettes/day in the second trimester

Variable	Intervention	Control	Difference (95% CI)
Singleton livebirths	1343	1357	
Birthweight (g)	3263 (542)	3229 (537)	+34 (-7 to +75)
Low birthweight			
<2500 g	99 (7.4%)	121 (8.9%)	-1.5% (-3.6 to +0.5)
≤ 1500 g	8 (0.6%)	9 (0.7%)	
Gestation at delivery (weeks)	39.7 (2.0)	39.5 (2.2)	
Preterm birth (<37 weeks)	109 (8.1%)	137 (10.1%)	
Fetal deaths (per 1000 livebirths)	26 (19.4)	21 (15.5)	
<20 weeks	5	4	
≥ 20 weeks	21	17	
Infant deaths (per 1000 livebirths)	5 (3.7)	10 (7.4)	
≤ 28 days	2	5	
>28 days <365 days	3	5	

Results are mean (SD) or *n* (%) values as appropriate

Table 3 shows the birthweight, gestational duration and fetal and infant deaths in the intervention and control groups. Overall, the mean birthweight was 34 g higher (95% CI -7 to +75 g), and the proportion of low birthweight babies was 17% lower among women in the intervention group, but neither of these differences was statistically significant. There were no statistically significant differences between the rates of deaths in the two groups.

The study plan included a provision for monitoring the extent of participation by the collaborating physicians. This was done by calculating the rate of securing repeat sera for cotinine

measurements in the intervention arm of the study. Table 4 divides the data into two strata, according to the extent of participation at each of the 139 sites. One stratum relates to the 50% of sites (70) which adhered most closely to the intervention protocol (i.e., the sites with the highest proportion of women in the intervention arm from whom a repeat blood sample for a cotinine measurement was collected) and the other stratum to the remaining half of sites (69). Since women were individually randomized at each site (the sites were not randomized), it was possible to compare the intervention and control groups within each stratum without introducing

Table 4. Effect of cotinine-assisted intervention on birthweight and gestational duration of singleton livebirths in women smoking ≥ 10 cigarettes/day in the second trimester by study site participation

Variable	High study site participation*			Low study site participation†		
	Intervention (<i>n</i> = 705)	Control (<i>n</i> = 685)	Difference (95% CI)	Intervention (<i>n</i> = 638)	Control (<i>n</i> = 672)	Difference (95% CI)
Mean initial serum cotinine (ng/ml)	164	168		173	168	
Birthweight (g) mean	3291	3225	+66	3238	3233	+5
(SD)	(523)	(556)	(+9 to +123)	(554)	(517)	(-53 to +63)
Low birthweight (%)	6.4	8.9	-2.5	8.3	8.7	-0.4
(<2500 g)			(-5.3 to 0.3)			(-3.5 to 2.6)
Gestation at birth (weeks)						
mean	39.7	39.6		39.6	39.5	
(SD)	(1.9)	(2.3)		(2.0)	(2.1)	

* Sites (*n* = 70) providing $\geq 47\%$ of the expected repeat samples for cotinine measurements

† Sites (*n* = 69) providing $\leq 46\%$ of the expected repeat samples for cotinine measurements

bias. Among the sites at which participation was high, the mean birthweight was 66 g higher ($P = 0.03$; 2-sided pooled t -test $t = 2.25$; 95% CI +9 to +123 g) and the proportion of low birthweight was 30% lower ($P = 0.08$; $\chi^2 = 3.1$) than in the control group. The difference was much less (5 g) and not statistically significant (95% CI -53 to +63 g) between the intervention and control groups at the sites where participation was low. The sites at which participation was high provided repeat sera for cotinine measurements from 454 women, but only 194 repeat sera were provided from the sites with low participation. The reasons why some physicians provided a smaller proportion of repeat blood samples than others is unclear; neither geographic distribution, size of practice, nor women's demographic characteristics could account for differences.

Of the 1343 women in the intervention arm with a singleton livebirth, 648 provided a repeat blood sample for serum cotinine measurement; 15.8% of the repeat cotinine levels were in the non-smoking category (<10 ng/ml), and another 17.5% showed reductions by more than half compared with the initial level, but were still consistent with smoking. This represents only 48% of the intervention group, however, and it is possible that compliance was less among those women not providing a follow-up sample. Regression analysis of the initial cotinine level and the change in cotinine level following intervention (defined as $\text{initial} - \text{final} / \text{initial} \times 100$) versus birthweight showed that each variable added significantly to the prediction of birthweight, given the other; a 1.68 g (SE 0.57, $P < 0.01$) increase in birthweight was associated with a 1% reduction in cotinine, and a 0.93 g (SE 0.24, $P < 0.01$) decrease in birthweight was associated with a 1 ng/ml increase in the initial serum cotinine.

Discussion

We have shown in a randomized clinical trial that encouraging women to give up smoking in the second trimester of pregnancy can reduce low birthweight delivery. The birthweight differences are consistent with published reports from two other recent randomized trials (Sexton & Hebel 1984; MacArthur *et al.* 1987). One randomized trial, reported by Donovan (1977) failed to demonstrate a birthweight difference, but the trial was small and lacked the statistical

power to exclude a useful effect. Taken as a whole, our study and those already published support a causal connection between smoking and low birthweight and demonstrate that prevention is feasible and effective. The smoking intervention we adopted in this study intentionally relies on physician office staff, rather than an outside team, since any anti-smoking programme, even if effective in a clinical trial, would need to be simple and economical to be widely adopted. The intervention regimen involves only two patient contacts, along with cotinine measurements to assist with the intervention as well as to judge compliance. The study was successful in obtaining physician office and clinic participation on a statewide basis (75%) and moderately successful in persuading participating sites to complete the intervention protocol.

Those participating sites where the intervention protocol was adopted best, as measured by the rate of providing follow-up blood samples, were also the sites where the impact on improving birthweight was greatest, a 66 g average increase was found in the intervention group over the control group, a statistically significant difference; the rate of low birthweight was reduced from 8.9% to 6.4%, a 30% reduction. Although this latter difference was not statistically significant ($P = 0.08$), we believe that this difference is unlikely to have arisen by chance, given the significant 66 g increase in mean birthweight. This average increase in birthweight is likely to result from a larger increase in birthweight among women who stopped smoking, combined with no increase in birthweight among those who continued to smoke. The stratified analysis we adopted avoided bias because women were randomized within site and the stratification was not based on the compliance of individuals with the regimen; within each site *all* the women, regardless of their adherence to the smoking intervention regimen, were included in the stratified analysis.

Our smoking intervention programme was very cost effective. The additional costs associated with the neonatal care of one low birthweight infant has been estimated at \$18 000 (Oster *et al.* 1988). The cost of preventing one low birthweight infant through our smoking intervention was about one-tenth of this.

Cotinine, the major metabolite of nicotine, is present in the blood, urine, and saliva of individuals who smoke or chew tobacco (Benowitz *et al.*

1983). Serum cotinine levels can reliably distinguish smokers from nonsmokers (Hill *et al.* 1983; Haddow *et al.* 1986). As the major metabolite of nicotine, cotinine is a specific indicator of tobacco intake. Unlike thiocyanate or carbon monoxide measurements, it is not confounded by dietary or environmental influences (Maleszewski & Boes 1955; Vogt *et al.* 1979; Dalferes *et al.* 1980; Hill *et al.* 1983). Cotinine has a biological half-life of about one day and, consequently, its level in body fluids represents a reliable time-averaged measure of the degree of nicotine intake over the previous few days (Benowitz *et al.* 1983). Further, the relation between cotinine levels in the second trimester and subsequent birthweight is already defined (Haddow *et al.* 1987). Cotinine is, therefore, an ideal measure of smoke intake for use in this study.

The smoking cessation intervention strategy reported by Sexton & Hebel (1984), which was also effective in increasing birthweight, relied on multiple personal contacts by specially trained staff from a central unit. Our strategy, by being simple and relying more on existing physician office personnel, can probably reach a wider population. Of course, for the strategy to be effective, it is necessary for physicians to adhere to the protocol. In this respect, it is of interest that, of the women who provided a follow-up sample for cotinine measurements, the proportion of women who stopped smoking or smoked less was similar, regardless of the extent of participation at each site. The main difference between the two strata of participation was simply the extent of participation, i.e., the proportion of women who provided a second sample. Effectiveness of this strategy may be enhanced by discovering ways to increase physician office participation, such as by sharing the knowledge that this approach to smoking cessation can be effective, or by using saliva, rather than blood, as the body fluid for follow-up cotinine measurement to avoid logistical difficulties with blood collection. Integrating smoking cessation activities with prenatal serum AFP screening could also provide access to these activities to most pregnant women in countries such as the US and UK where AFP screening has, in general, become a routine part of antenatal care. Probably no other single simple measure can achieve as much in the prevention of low birthweight.

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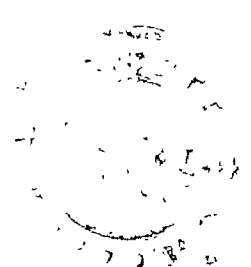
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Early amniocentesis: alphafetoprotein levels in amniotic fluid, extraembryonic coelomic fluid and maternal serum between 8 and 13 weeks

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Abstract

Objective—The aim was to establish a normal range of alphafetoprotein (AFP) concentrations in amniotic fluid from 8 to 12 weeks gestation, and to determine any difference between AFP levels in amniotic fluid and extraembryonic coelomic fluid.

Design and subjects—150 women had a transvaginal ultrasound guided amniocentesis before termination of an apparently normal first trimester pregnancy. Separately identified samples of amniotic fluid and extraembryonic coelomic fluid were obtained and assayed by radioimmunoassay for AFP.

Results—In amniotic fluid, very high levels of AFP were present at 8 weeks, levels falling rapidly up to 10 weeks after which there was a slight rise. Thus over the period 8 to 10 weeks, there was a significant inverse correlation between amniotic fluid AFP and gestational age ($r = 0.67$; $P < 0.001$). In extraembryonic coelomic fluid, by contrast there was no trend in AFP relative to gestational age.

Conclusions—The rapidly changing levels of AFP from 8 to 10 weeks as well as the small volume of the amniotic cavity makes the use of amniocentesis impracticable before 11 weeks gestation. The lack of any relation between AFP levels in amniotic fluid and extraembryonic coelomic fluid emphasises the importance of identifying the site of amniocentesis in the first trimester.

The measurement of alpha-fetoprotein (AFP) or acetylcholinesterase (AChE) in amniotic fluid is an established method of diagnosis of neural tube defects in the second trimester of preg-

nancy. More recently, the use of early amniocentesis has been investigated (Drugan *et al.* 1988; Johnson & Godmilow 1988; Muller *et al.* 1989). Amniotic fluid AChE does not appear to be a reliable marker of neural tube defects before 11 completed weeks gestation (Burton *et al.* 1989; Muller *et al.* 1989). If measurement of AFP is to be used, then normal levels of amniotic fluid AFP in the first trimester must be further established; levels of AFP from 11 weeks of pregnancy are known (Brumfield *et al.* 1990; Crandall *et al.* 1989; Drugan *et al.* 1988), but there is little information before this time.

The use of high resolution vaginal ultrasound demonstrates clearly that two fluid compartments surround the first trimester fetus: the amniotic cavity and the extraembryonic coelom

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(Fig. 1). In the late first trimester, significant biochemical differences between the two fluid compartments have been identified for a number of placental/decidual compounds (Wathen, unpublished data) but not for AFP (Wathen *et al.* 1991). However, as the fetus lies in the amniotic cavity, the levels of AFP might be higher in this site relative to the extraembryonic coelom when there is a neural tube defect. If this is the case, the origin of the sample obtained at amniocentesis would need to be established accurately. In the present study, direct ultrasound guided transvaginal amniocentesis was carried out prior to termination of pregnancy in 105 apparently normal pregnancies between 8 and 13 weeks in order to obtain separately identified samples of amniotic fluid and extraembryonic coelomic fluid for measurement of AFP.

Subjects and methods

In total 105 women consented to ultrasound guided transvaginal amniocentesis before termination of apparently normal pregnancies between 8 and 13 weeks. Consent was also obtained for collection of 10 ml maternal blood before induction of anaesthesia. Transvaginal ultrasound was performed using an Aloka SSD-620 with a 5 MHz vaginal probe that had a 60° effective angle of view. Using full aseptic technique, the probe was sited in the upper vagina so as to obtain a clear view of the pregnancy. Fetal viability was assessed and the crown rump length (CRL) recorded. Using the procedure described previously (Wathen *et al.* 1991), transvaginal amniocentesis was performed so as to obtain a sample of fluid from the extraembryonic coelom and then from the

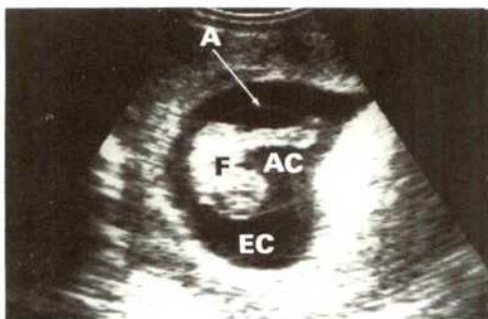


Fig. 1. An ultrasound image of a 9 week fetus showing the fetus (F), amniotic cavity (AC), amnion (A) and extraembryonic coelom (EC).

amniotic cavity. Bimanual examination of the uterus and injection of oxytocic agents were delayed until after amniocentesis so as to avoid possible alteration of AFP levels. In the earlier pregnancies (8–9 weeks) the volume of the amniotic cavity in some women was so small as to preclude reliable sampling. As pregnancy advances, the amniotic cavity expands to obliterate the extraembryonic coelom at about 12–13 weeks gestation. For this reason, it was not possible to obtain a sample of extraembryonic coelomic fluid in all of the late first trimester amniocenteses. All samples were stored at -20°C until assayed by radioimmunoassay for AFP (Kitau *et al.* 1988).

In this study, CRL measurement was used to establish gestational age which was allocated according to the number of completed weeks; thus a gestational age of 8 weeks includes CRL measurements of 8 weeks plus 0 days to 8 weeks plus 6 days.

The protocol for this study was approved by the ethics committee of St Bartholomew's Hospital, London.

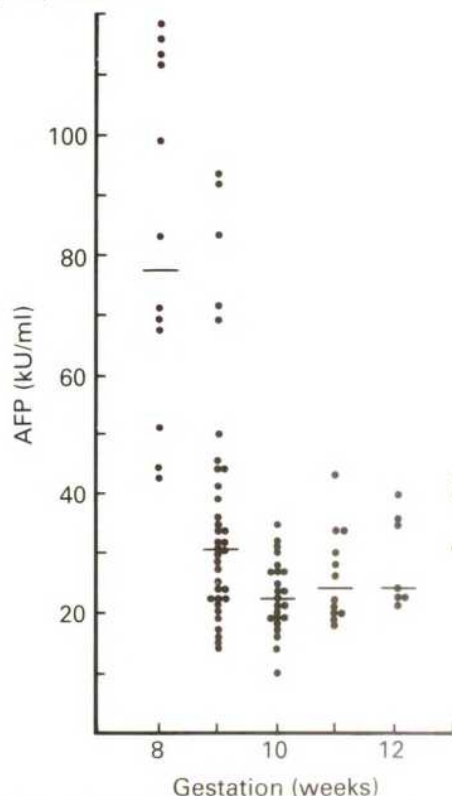


Fig. 2. AFP levels in amniotic fluid at 8–13 weeks gestation. The horizontal bars indicate the median level at each week.

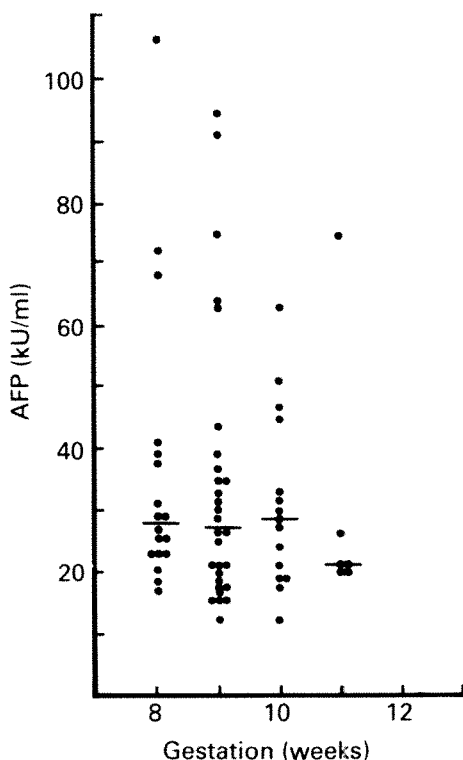


Fig. 3. AFP levels in extraembryonic coelomic fluid at 8–13 weeks gestation. The horizontal bars indicate the median level at each week.

Results

The levels of AFP in amniotic fluid, extraembryonic coelomic fluid and maternal serum are shown in Figs. 2–4 and in Table 1. In amniotic fluid, very high levels of AFP were present at 8 weeks gestation and then fell rapidly up to 10 weeks gestation. Thus, over the period 8–10 weeks, there was a highly significant inverse correlation between amniotic fluid AFP and gestational age ($r = 0.67$; $P < 0.001$). From 11 to 13 weeks, there was a small rise in AFP levels. In the extraembryonic coelomic fluid, by contrast, there was no trend in AFP relative to gestational age (Table 1; Fig. 3). There was no correlation between AFP levels in amniotic fluid and extraembryonic coelomic fluid. In maternal serum, there was a significant increase ($r = 0.57$; $P < 0.001$) in AFP levels with gestation (Table 1; Fig. 4). Although the amniotic cavity could be identified in all the pregnancies at 8 weeks, the volume was too small to be sampled accurately in eight women (40%). The extraembryonic coelom could not be identified by ultrasound in one

of the three pregnancies at 13 weeks and in three of the seven at 12 weeks. In the remaining women at 12 and 13 weeks, a small extraembryonic coelom was identified but the volume was too small to sample reliably.

Discussion

The yolk sac and the liver are closely related embryologically and both produce AFP in early pregnancy (Gitlin & Pericelli 1970; Ishiguro *et al.* 1983; Shi *et al.* 1985). Fetal serum levels of AFP rise from 6 weeks to a maximum at approximately 13 weeks and then fall rapidly (Gitlin & Boesman 1966). No previous study has reported on significant numbers of AFP levels in amniotic fluid before 11 weeks of gestation. From 11 weeks, amniotic fluid levels of AFP show a similar pattern to those in fetal serum, levels rising to 13 weeks and then falling (Brumfield *et al.* 1990; Crandall *et al.* 1989; Drugan *et al.* 1988). We now demonstrate high levels of AFP in amniotic fluid at 8 weeks, which fall rapidly up to 10 weeks after which there is a small rise. The

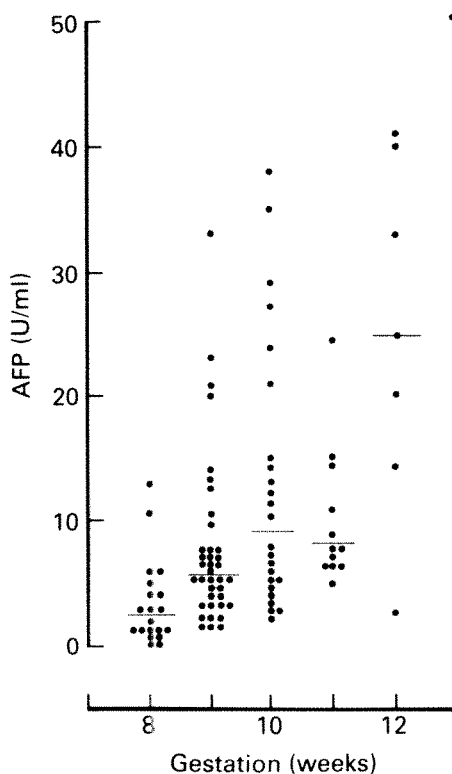


Fig. 4. AFP levels in maternal serum at 8–13 weeks gestation. The horizontal bars indicate the median level at each week.

Table 1. Levels of AFP in amniotic fluid, extraembryonic coelomic fluid and maternal serum by gestational age

AFP	Gestational age (weeks)					
	8	9	10	11	12	13
Amniotic fluid (kU/ml)						
Number	12	35	23	12	7	3
10th centile	43.3	15.8	15.2	18.8	15.2	
Median	77.2	30.0	22.5	24.2	24.0	
90th centile	115.8	70.1	30.7	34.8	37.7	
Extraembryonic coelomic fluid (kU/ml)						
Number	18	29	15	6	—	—
10th centile	17.8	16.4	15.1	12.0		
Median	28.3	27.1	29.1	21.4		
90th centile	68.8	65.1	49.0	45.6		
Maternal serum (U/ml)						
Number	20	38	24	12	7	3
10th centile	0.3	2.2	2.9	5.2	1.7	
Median	2.3	5.7	9.1	7.8	25.0	
90th centile	6.0	14.8	28.2	14.9	40.3	

levels of AFP in amniotic fluid at any gestation are only a small percentage of the levels found in fetal serum (Gitlin & Boesman 1966).

We present three possible explanations for the relatively high levels of amniotic fluid AFP in early pregnancy. First, excessive leakage of AFP in urine. Fetal urine is the main source of amniotic fluid AFP (Seppala & Ruoslahti 1972). It is possible that there is excessive leakage of AFP from the immature metanephros, AFP levels dropping rapidly as renal function develops. Second, impaired AFP clearance from the amniotic cavity. Alpha-fetoprotein is largely degraded by the process of swallowing and digestion (Pritchard 1965). Absence of, or immaturity of these mechanisms in early pregnancy may alter the normal turnover of AFP, resulting in high levels. Furthermore, re-absorption from the amniotic compartment may increase as the extraembryonic coelom disappears and the fetal membranes relate more closely to the decidua. The third possible explanation, transudation of AFP from the bowel, the postulated cause of high amniotic fluid AFP levels in cases of exomphalos (Brock 1976), is unlikely. Although the midgut is extra-abdominal until approximately the tenth week of pregnancy (Hamilton & Mossman 1972), it is exposed to the extraembryonic coelom and not to the amniotic fluid. There is no trend in AFP levels in extraembryonic coelomic fluid relative to gestational age (Fig. 3).

The possibility of early amniocentesis for the

diagnosis of neural tube defects has been discussed. However, the rapidly changing levels of AFP from 8 to 11 weeks of pregnancy, as well as the small volume of the amniotic cavity almost certainly makes the use of amniocentesis impracticable before 11 weeks gestation. The absence of any relation between AFP levels in amniotic fluid and extraembryonic coelomic fluid in this study further emphasises the importance of identifying the exact site of amniocentesis in the first trimester.

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Doppler investigation of uteroplacental blood flow resistance in the second trimester: a screening study for pre-eclampsia and intrauterine growth retardation

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Abstract

Objective—To assess the screening properties of a mid-trimester uteroplacental Doppler scan in a normal unselected population.

Design—A cross-sectional study measuring an averaged resistance index (AVRI) from four sites (left and right uterine and arcuate arteries) with continuous wave Doppler ultrasound.

Setting—Routine booking ultrasound, King's College Hospital, London.

Subjects—977 women at 16-24 weeks gestation.

Main outcome measures—Intrauterine death, birthweight, pregnancy-induced hypertension (PIH), antepartum haemorrhage.

Results—There was a 96.5% follow-up. Pregnancies with high AVRI values had a higher prevalence of proteinuric hypertension, placental abruption, small-for-gestational-age babies, and fetal loss. When AVRI was >95th centile, the overall risk of pregnancy complications was 67%, and the risk of a severe complication was 25%. However, the sensitivity of the test for these complications was only 13% and 21% respectively. The risk for an individual woman with a high AVRI of developing a complication was increased by up to 9.8 times.

Conclusion—Although Doppler screening does detect a unifying defect leading to perinatal death, pre-eclampsia, growth retardation and placental abruption, the predictive values do not yet justify its introduction as a routine test.

Although pre-eclampsia and intrauterine growth retardation (IUGR) are major causes of maternal and perinatal mortality and morbidity, the conditions are poorly defined and the underlying pathology ill-understood. Morphological studies have suggested a failure of trophoblastic invasion as a common underlying cause (Brossens *et al.* 1977; Khong *et al.* 1986) and this may be manifest in early pregnancy as an increased resistance to flow in the uteroplacental circula-

tion as measured by Doppler ultrasound (McParland & Pearce 1988).

Although seven Doppler studies screening for these complications have been reported (Campbell *et al.* 1986, Arduini *et al.* 1987; Schulman *et al.* 1989, Hanretty *et al.* 1989; Newnham *et al.* 1990; Jacobson *et al.* 1990; Steel *et al.* 1990), they produced widely varying results and no unifying conclusion can be drawn. There are a variety of possible explanations for the great discrepancies.

The studies have mostly used small numbers ranging from 60 (Arduini *et al.* 1987) to 535 (Newnham *et al.* 1990), although Steel *et al.* (1990) recruited 1198 women

They have used different methods of insonating the uteroplacental circulation. Both pulsed wave (Campbell *et al.* 1986; Arduini *et al.*

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1987; Jacobsen *et al.* 1990) and continuous-wave Doppler ultrasound (Schulman *et al.* 1989, Hanretty *et al.* 1989; Newnham *et al.* 1990; Steel *et al.* 1990) have been used to study the uterine artery (Schulman *et al.* 1989), the arcuate artery (Campbell *et al.* 1986) and the uteroplacental bed beneath the placenta (Newnham *et al.* 1990), while others sampled from anywhere on the uterine vascular tree (Hanretty *et al.* 1989).

Different absolute cut-off levels of resistance index (RI) were used by most investigators, ranging between 0.52 and 0.62, despite the fact that RI is known to fall steeply with gestation in the second trimester (Cohen-Overbeek *et al.* 1985; Bewley *et al.* 1989). Only two investigators used a cut-off >95th centile for gestation (Hanretty *et al.* 1989; Newnham *et al.* 1990). This may explain why the frequency of abnormal waveforms varied between 3.5% (Schulman *et al.* 1989) and 33% (Arduini *et al.* 1987). In the study of Campbell *et al.* (1986) 40% of an apparently unselected group had an RI >2 SDs above the mean for normal women.

The sample groups that have been studied were not all representative of normal populations. Some recruited high risk women (Arduini *et al.* 1987; Jacobsen *et al.* 1990) or primigravidae (Steel *et al.* 1990), while others tried to choose randomly from the ultrasound clinic (Campbell *et al.* 1986) or the antenatal clinic (Hanretty *et al.* 1989). In one study, although selecting patients randomly from the ultrasound department, a high prevalence of complications of 25% was found (Campbell *et al.* 1986). In another study, after recruitment from the antenatal clinic, 46% of women were admitted or investigated during the pregnancy, 25% developed pregnancy-induced hypertension (PIH), 24% were delivered electively and 36% had instrumental deliveries (Hanretty *et al.* 1989). A further study achieved recruitment of only 46% of the total pregnant population (Schulman *et al.* 1989). Despite having the loosest definition of site, Hanretty *et al.* (1989) failed to obtain readings from the uteroplacental circulation at 26 weeks in 18%. The study group may thus have become biased even if the subjects had been randomly selected.

Non-comparable definitions of complications were used. Investigators have used varying and different definitions of pre-eclampsia, IUGR and poor pregnancy outcome as well as combining the outcomes in unique ways. One study looked at PIH without considering IUGR separ-

ately (Arduini *et al.* 1987). Some studies considered two readings of blood pressure >140/90 as PIH (Steel *et al.* 1988; Arduini *et al.* 1987) and then examined whether it was accompanied by proteinuria (Steel *et al.* 1990), whereas others included proteinuria and hyperuricaemia in the definition of pre-eclampsia (Jacobsen *et al.* 1990). In one study a patient was classified as having PIH if, 'following a blood pressure recording of $\geq 140/90$, the obstetrician arranged for further investigation or treatment' (Hanretty *et al.* 1989). Most studies used a birthweight below the 10th centile to define IUGR although one used an ultrasound abdominal circumference of more than 2 SDs below the mean (Steel *et al.* 1990). One study combined abnormal CTG, low cord pH and low Apgar score for the definition of perinatal asphyxia (Campbell *et al.* 1986). Another stated that its 'criteria for this diagnosis were arbitrary' and used these features separately. Fetal hypoxia was diagnosed by an obstetrician retrospectively (Newnham *et al.* 1990).

The missing cases due to exclusions and losses varied from 0% (Arduini *et al.* 1987; Hanretty *et al.* 1989) to 21% (Steel *et al.* 1988). Those women who were lost to follow-up (ending their pregnancies as an emergency elsewhere, whose notes were sequestered at some point or who moved) may have been a different group than those with known outcomes.

Only two studies stated that the assessment of outcome was made 'blind', separate from knowledge of the test result (Newnham *et al.* 1990; Jacobsen *et al.* 1990). Although most did not give the results to the clinicians, one gave the results to both the patients and clinicians (Schulman *et al.* 1989), and another repeated the Doppler test if the results were abnormal (Steel *et al.* 1990), thus potentially giving both an inkling of the result.

The aim of the present study was to determine the ability of a second trimester continuous wave Doppler examination of the uteroplacental circulation to predict pre-eclampsia and small-for-gestational-age infants (SGA), and to quantify the predictive properties of such a test. In this paper, the methodological problems have been overcome by having a large number of subjects, an overall RI taken from fixed sites, a cut-off for abnormality that changes with gestation, a representative population, a range of cut-offs for 'abnormality', a high follow-up rate, and a variety of abnormal outcomes that were assessed

'blind' and analysed both separately and together.

Subjects and methods

Signals were collected using a 4 MHz CW probe (Doptek, Chichester, UK) from four fixed sites on the uterus, left and right 'arcuate' and left and right 'uterine' (Bewley *et al.* 1989). Women were recruited consecutively when attending for their routine booking scan at 16–24 weeks gestation. No results were revealed to the women or the clinicians. No action was taken on the basis of any readings. The study had ethics committee approval.

At King's College Hospital (KCH), booking and delivery data are routinely entered into the perinatal computer by the attending midwife. Searches for missing data or addresses included the antenatal filing cards, the hospital microfilm, hospital records department and the ultrasound scan card. In those cases without information or delivery out of the area, two postal enquiries were made to both the woman, with a stamped addressed envelope, and her general practitioner. Information about neonatal outcome was obtained from the neonatal unit ledger or the baby notes. Coding forms were completed with booking and delivery details for each subject by a coder using standard coding instructions. The data were then entered into the University of London Computer (Amdahl 5890/300, SPSS statistical package). The data were entered twice and the computer files compared to pick up transcription errors. A gestation check was performed and validation checks were made to pick up obvious coding errors.

Medical notes were retrieved and reviewed in detail if there was any deviation from normal indicated on the computer delivery form (i.e., all women with preterm delivery, hypertension, antepartum haemorrhage, antenatal admission, emergency caesarean section, 'abnormal CTG', operative delivery for fetal distress, neonatal unit admission, maternal disease and anything else suspicious). Notes were collected for 24.3% of cases and reviewed by one of the authors (S.B.). This process was kept separate from knowledge of the initial test results by leaving the test forms undisturbed in a locked filing cabinet for the duration of the study. Three independent obstetricians later coded medical diagnoses. Discrepancies in coding were reviewed by all three in conjunction with the coding forms

and instructions to decide on the final assignment of diagnoses.

Hypertension was defined as two recordings of diastolic BP ≥ 90 mmHg, 4 h apart, or one reading of ≥ 110 mmHg at any stage of pregnancy (Davey & MacGillivray 1988). If hypertension was noted before 20 weeks it was defined as chronic hypertension. Pregnancy-induced hypertension was defined as hypertension appearing for the first time after 20 weeks gestation and categorized as proteinuric or nonproteinuric. Significant proteinuria was considered as >150 mg/24 h, or $>+$ on dipstick urine testing, and nonsignificant if it disappeared on repeat testing. Severe proteinuric PIH was defined as a diastolic BP ≥ 110 mmHg and proteinuria >500 mg/24 h or $\geq++$ on Albustix (and a rise of $\geq 30/25$ mmHg if hypertension was present before 20 weeks gestation).

Antepartum haemorrhage (APH) was defined as bleeding from the genital tract (>5 ml) after 28 weeks gestation. The cause was considered to be placental abruption if there was proven retroplacental clot or a general disturbance of coagulation.

Fetal loss, or intrauterine death (IUD) was defined as the death of a fetus between the blood flow screening scan and delivery (excluding termination of pregnancy).

Actual birthweight (Bwt) was expressed as a number of SDs from the mean expected weight for gestation, compared to the hospital population >36 weeks and to a preterm infant weight chart <36 weeks (Gairdner & Pearson 1971). Babies were considered small-for-gestational-age (SGA) and under the 3rd, 5th, and 10th centiles if they were >1.96 , >1.645 or >1.28 SDs respectively below the mean expected weight for gestation.

Operative delivery for fetal distress (ODFD) was based on the indication for delivery by forceps, or caesarean section, that is, the clinical judgement of the operator at the time. Birth asphyxia was not defined due to the difficulty in having an agreed definition for this 'entity' and the problems in interpreting CTGs (Sykes *et al.* 1982), Apgar score and pH (Ruth & Rarvio 1988). Where information was unclear or only partial, a final coding diagnosis such as 'hypertension—unknown proteinuria or severity' was made. Uncertain diagnoses were excluded from the final analysis for that particular outcome.

Of 1022 women approached in the ultrasound department, 1018 agreed to participate in the

study. Statistical analysis was performed in 925 cases, the remainder being excluded for a variety of reasons (Fig. 1). Outcome losses were small and data were available for 96.5% (943/977) of the population. The 14 twin pregnancies were excluded from the screening analysis as the interpretation of complications was too complex.

To determine that no peculiarities occurred during selection of subjects or with the loss of missing data, two comparisons were made; with the previous year of deliveries at KCH; and the missing cases were compared with the known outcome cases. There were slightly more Caucasians (60% vs 54%) in the study than the general delivered population, which might be explained by later bookings of African women. The 34 cases with lost data were younger and smoked more but this was not of statistical nor clinical significance.

Of the 925 women, 913 (98.7%) were delivered of a live baby. Twelve had an intra-uterine death (1.3%) (three at <24 weeks, two at 24–28 weeks and seven at >28 weeks) and there were three neonatal deaths (0.3%).

Resistance index (RI = systolic peak – end-diastolic trough/systolic peak) (Pourcelot 1974) was calculated. The averaged value from the four uteroplacental sites was called AVRI. Worst RI was the highest value, and best RI the lowest. AVRI was normally distributed with constant variance at all gestations, and the relation between AVRI and gestation was linear. AVRI was regressed on gestational age and the 90% prediction interval for individual values of AVRI was calculated (Draper & Smith 1966). The limits of this interval provide the 5th and 95th centiles for AVRI for each gestational

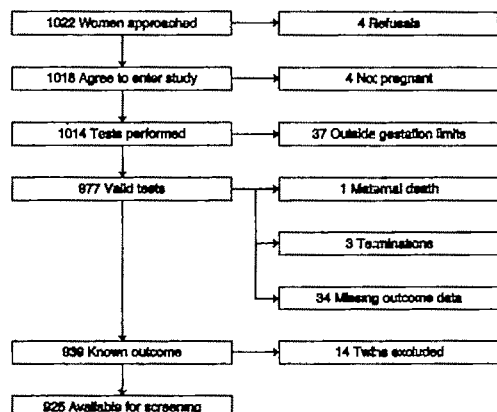


Fig. 1. Flow diagram showing subject numbers.

age. We checked that a quadratic regression did not significantly explain more of the variation in the data than linear regression. AVRI was found to change significantly with gestation ($AVRI = 0.669 - 0.00109$ days gestation, $n = 975$, residual SD = 0.091, $p = <0.0001$). Having constructed the reference range (i.e., the 5th and 95th centiles) (Fig. 2), individual AVRI values were expressed as a number of standard deviations from the expected mean for gestation (δ AVRI). The values were considered to be in the highest 2.5%, 5% and 10% of the population if the values of δ AVRI were >1.96 , >1.645 or >1.282 SDs from the mean respectively. For each case, a δ AVRI value was used to predict various outcomes using different cut-offs in turn. In this way, the screening potential of uteroplacental Doppler was assessed.

The numbers of true positives (TP), false positives (FP), true negatives (TN), false negatives (FN), sensitivity, specificity, positive predictive value, negative predictive value and prevalence for each complication for a variety of cut-offs were calculated. The relative risk

$\left[\frac{TP}{FN} \frac{FN + TN}{TP + FP} \right]$ is the increased risk of having disease that a test positive subject has compared to a test negative one.

To define the risk to any particular pregnancy

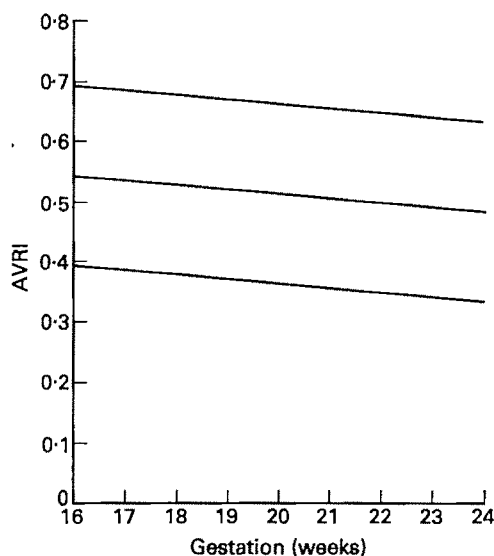


Fig. 2. Reference range of AVRI (averaged value of resistance index from four uteroplacental sites) according to gestational age showing mean, 5th and 95th centiles ($n = 975$).

Table 1. The prediction of different separate complications using Doppler test AVRI >95th centile for gestational age as cut-off for abnormality

Outcome	Prev (%)	TP	FN	FP	TN	SE (%)	SP (%)	PPV (%)	NPV (%)	RR	n*
IUD	1.3	3	9	51	862	25	94	6	99	5.4	925
Abruptio	0.9	3	5	50	864	38	95	6	99	9.8	922
APH (all)	4.0	5	32	48	837	14	95	9	96	2.6	922
Nonpr PIH	5.5	5	45	46	821	10	95	10	95	1.9	917
Pr PIH	4.6	10	32	41	834	24	95	20	96	5.3	917
SGA <3rd	3.3	6	24	46	837	20	95	12	97	4.0	913
SGA <5th	5.7	10	42	42	819	19	95	19	95	4.0	913
SGA <10th	12.9	18	100	34	761	15	96	35	88	3.0	913

Abbreviations: AVRI, averaged resistance index from four sites; IUD, intrauterine fetal death; APH, antepartum haemorrhage; Pr PIH, proteinuric hypertension; Nonpr PIH, nonproteinuric hypertension; SGA, small-for-gestational age; Prev, prevalence; TP, true positive; FP, false positive; TN, true negative; FN, false negative; PPV, positive predictive value; NPV, negative predictive value; RR, relative risk; SE, sensitivity; SP, specificity.

*Numbers do not all equal 925 if there were insufficient data for diagnosis.

of developing complications the outcomes were also amalgamated into two groups. Any included all pregnancies with SGA <10th centile or any PIH or any APH or IUD or ODFD, as defined above. Severe represented severest disease and a more stringent definition of abnormal; SGA <3rd centile or severe proteinuric hypertension or placental abruption or IUD. Women with 'severe' complications are included in the 'any' group.

AVRI had a higher correlation with δ Bwt ($r = -0.26$) than worst RI ($r = -0.22$) or any of the individual vessel RI values ($r = -0.14$ to -0.21) so it was chosen as the screening variable. By being a mean of four values, it is more precise than single values, and may give a better overall picture of the complex circulation than one site (Bewley *et al.* 1989). The intra-observer coefficient of variation for AVRI was measured by taking three sets of readings from 11 subjects and was 3.9%. In the Tables and the Results section, calculations are made using the total avail-

able data for any variable which may not always equal 925.

Results

The prediction of different separate complications using AVRI >95th centile as a cut-off is shown in Table 1. The sensitivity varies between 10% and 38%. The relative risk of a test positive woman developing complications, as opposed to a test negative woman, ranged from 1.9 to 9.8 and was higher for more severe disease.

The positive predictive value of AVRI >95th centile was 67% for any complication and 25% for a severe complication (Table 2).

Screening characteristics were compared using different variables (Table 3) AVRI was more accurate than worst RI and best RI in the prediction of complications.

The test can be used with any cut-off of AVRI (Table 4), but the specificity falls below 73% before the sensitivity reaches 50% for severe

Table 2. The prediction of combinations of complications using AVRI >95th centile for gestational age as cut-off for abnormality

Outcome	Prev (%)	TP	FN	FP	TN	SE (%)	SP (%)	PPV (%)	NPV (%)	RR	n*
Any†	30.3	35	241	17	619	13	97	67	72	2.4	912
Severe‡	7.0	13	49	38	789	21	95	25	94	4.4	889

For abbreviations, see Table 1.

*Numbers do not all equal 925 if there were insufficient data for diagnosis.

†Any includes SGA <10th centile, PIH, APH, IUD and operative delivery for fetal distress

‡Severe includes SGA <3rd centile, severe proteinuric hypertension, abruption and IUD.

Table 3. The prediction of complications using different 95th centile Doppler tests as cut-off for abnormality

δ RI >95th	SGA <10th		Proteinuric hypertension		Any*		Severe*	
	SE(%)	SP(%)	SE(%)	SP(%)	SE(%)	SP(%)	SE(%)	SP(%)
AVRI	15	96	25	95	13	97	21	95
Worst RI	14	95	22	95	11	96	13	94
Best RI	10	95	17	95	10	96	16	95

Abbreviations: δ RI >95th, resistance index >95th centile for gestational age; AVRI, averaged RI from four sites (left and right arcuate and uterine), SE, sensitivity; SP, specificity.

*For definitions of Any and Severe complications see Table 2 and text

complications. Table 4 also shows a comparison using the original cut-off of worst FVW 0.58 (Campbell *et al.* 1986).

The test was marginally better at predictions in primigravidae, and much better in Afro-Caribbean women (Table 5).

Discussion

In our study, a large number of women, representative of the local pregnant population, were recruited, with a 96.5% follow-up rate. The predictions of disease fall short of the initial optimistic results of Campbell *et al.* (1986) but are in contrast to the entirely negative results of Hanretty *et al.* (1989).

A new and different methodology was employed in that an overall, four site, averaged RI (AVRI) was calculated. This had the highest correlation with δ Bwt, consistent with it giving an indication of the resistance in the whole uter-

ine circulation. Other investigators have used the average of two uterine flow velocity waveforms (FVW) (Schulman *et al.* 1986), the worst FVW (Campbell *et al.* 1986; Arduini *et al.* 1987) or even the best FVW (Hanretty *et al.* 1989) as the marker of abnormality. In the present study, there was little difference between the screening variables of AVRI and worst RI. Best RI was less effective as a predictor of complications and its use should be discouraged.

The cut-off of >95th centile for gestation was considered to be a practical one for abnormality, and although the sensitivities are low, the specificities are high. Using the old cut-off of 0.58 (Campbell *et al.* 1986) gives sensitivities comparable to those reported by others although the specificities are lower. By not choosing one particular cut-off for 'abnormal FVW' a range of predictions can be made (Table 4).

Our findings that abnormal FVWs precede the development of SGA and PIH confirm those of

Table 4. The prediction of complications using (a) different centiles of δ AVRI as cut-off for abnormality, and (b) worst RI >0.58

Centile δ AVRI	SGA >10th		Proteinuric hypertension		Any*		Severe*	
	SE(%)	SP(%)	SE(%)	SP(%)	SE(%)	SP(%)	SE(%)	SP(%)
97.5	11	98	15	97	8	99	13	97
95	15	96	25	95	13	97	21	95
90	22	92	30	91	17	93	29	91
85	32	89	35	87	23	90	37	88
80	36	83	47	82	28	85	44	82
75	42	78	52	77	34	80	45	77
70	47	74	55	72	38	75	50	73
Worst RI >0.58	82	38	82	36	73	39	77	37

Abbreviations: δ AVRI, Averaged resistance index related to centile for gestational age, Worst RI, highest RI from four uteroplacental sites, SGA, small-for-gestational age, SE, sensitivity; SP, specificity.

*For definitions of Any and Severe complications see Table 2 and text.

Table 5. A comparison of the prediction of complications in primigravidae vs multigravidae and black vs white women using AVRI >95th centile for gestational age as cut-off for abnormality

Parity/ race	n	SGA <10th			Proteinuric hypertension		
		Prev(%)	SE(%)	SP(%)	Prev(%)	SE(%)	SP(%)
0	448	16.4	19	96	6.0	26	95
≥1	476	9.6	9	96	2.7	23	95
Afro-Caribbean	254	13.7	15	95	5.1	46	95
Caucasian	564	11.9	10	96	4.4	8	95
		Any*			Severe*		
		Prev(%)	SE(%)	SP(%)	Prev(%)	SE(%)	SP(%)
0		38.3	13	97	7.8	18	94
≥1		23.2	13	97	6.2	25	97
Afro-Caribbean		33.2	14	97	10.7	27	95
Caucasian		29.5	10	97	5.1	11	96

Abbreviations: AVRI, Averaged resistance index from four sites; Prev, Prevalence; SE, sensitivity, SP, specificity

*For definitions of Any and Severe complications see Table 2 and text.

other workers. However, the predictions for proteinuric hypertension were clearly better than for non-proteinuric hypertension and it would seem prudent for investigators to distinguish between the two. Although abnormal Doppler findings have been noted in the months preceding a placental abruption (Uzan *et al.* 1989), the early prediction is new. Newnham *et al.* (1990) found a relation only between an abnormal FVW and hypoxia. The discrepancy may be due to the fact that a different part of the circulation was insonated under the placenta. The entirely negative results of Hanretty *et al.* (1989) can be accounted for by a difference in technique.

Our predictive values rose with increasing δ AVRI (Table 4). Thus, in the group with AVRI >95th centile, a woman had a 25% chance of a very serious complication, and a 67% chance of one probably requiring investigation or admission to hospital (Table 2). Steel *et al.* (1990) also found that the test identified the severest forms of hypertensive disease in pregnancy. So, the test defines well a high-risk group of women. This may be acceptable for selecting a group of women for research purposes, increased surveillance or treatment. However, in routine practice most women with disease would be missed. False reassurance may lull the woman and clinician into complacency and could form the basis for litigation for missed disease.

The test can have an improved sensitivity by use of a lower threshold for the definition of

abnormality. However, the specificity fell to below 73% before the sensitivity reached 50% for severe complications (Table 4). This means that over a quarter of the population have to be defined as abnormal even to pick half of those with disease. This would not support the introduction of Doppler studies on a routine basis. However, the finding of improved sensitivity in primigravidae and Afro-Caribbean women suggests that there may be populations for whom routine Doppler studies could be considered. These findings need to be confirmed. There are differences in hypertension between races (World Health Organization 1988), although they may not be apparent at 16–24 weeks gestation. It may be that in Afro-Caribbean women, pre-eclampsia is more severe, with higher AVRI values, and therefore more disease is correctly predicted. Alternatively, more hypertension in Caucasians is labelled pre-eclampsia when it is not associated with abnormal uteroplacental circulation and may be chronic hypertension.

The overlap in second trimester AVRI between normal and abnormal outcome pregnancies could be due to a number of reasons. Firstly, there is variability in the test but, in the form of AVRI, the coefficient of variation at 3.9% is acceptable. All the readings were recorded by one person and it might be postulated that errors would increase with multiple observers. Secondly, it may be that the test is accurate but that uteroplacental resistance itself

is not static and varies in both normal and abnormal pregnancies. Thirdly, RI provides a crude analysis of the waveform. Attempts have been made to define the shape of the waveform and use the information included in the distribution of the frequencies but it is unclear as yet whether any other index is better.

Fourthly, the definitions of outcome may be inadequate. The outcomes are actually heterogeneous mixtures of different aetiologies. For example, not all APH is caused by placental abruption. Pre-eclampsia is not the cause for all cases of PIH. In early onset pre-eclampsia, underlying renal disease may be undiagnosed and add to the false negative rate (Ihle *et al.* 1987). The small-for-dates infant is the result of one of a number of pathologies which include uterine or placental 'insufficiency'. A higher relative risk and increasing sensitivity with decreasing centiles of δ Bwt was found (Table 1). This might be considered a kind of 'dose response' and the Doppler test may be correctly distinguishing the diagnosis of IUGR. Affected babies are predominantly represented in the SGA <3rd centile group rather than normally grown small babies which often appear in the SGA <10th centile group. Doppler may be identifying potentially 'starved' babies (as not all babies end up below the 10th centile) rather than those ending with a low absolute birthweight. Unfortunately, we cannot assess the growth potential of an individual fetus or 'loss of expected weight' that might be more related to uterine blood supply and fetal damage.

Fifthly, the mother and fetus may have mechanisms which compensate for, or overcome, the restricted uterine blood supply. There is a functional reserve capacity of the placenta. Loss of a third of the villous parenchyma can take place without an effect on fetal growth, development or viability (Fox 1983). A false positive test might be explained by compensatory mechanisms that overcome deficient placentation. The placenta may be able to redistribute blood locally, away from scantily supplied and perfused segments. Delivery may supervene before the development of a stillbirth or pre-eclampsia.

Sixthly, there may be much more overlap of normal and abnormal FVWs at this gestation than later in pregnancy. Some normal pregnancies may still not have reached their minimum resistance by 20, or even 24 weeks gestation. Seventhly, there may be false positive and negative tests entirely due to biological vari-

ance. Although previous studies suggest that uteroplacental FVWs are not greatly influenced by day to day variability, circadian changes or meals, smoking or exercise (Hastie *et al.* 1988; Pearce *et al.* 1988; Morrow *et al.* 1988; Moore *et al.* 1988) and that the test is reproducible, only normal pregnancies have been studied in this way. There may be much greater variations or instability associated with the pathological pregnancy. Abnormal uterine waveforms may sometimes become apparent later in pregnancy, after the time of the screening test, especially if vasoconstriction of muscular arteries is aggravated by the release of vasoactive compounds such as thromboxane. A false negative test might also arise during sampling of the large uteroplacental circulation if there is a mixed population of vessels.

It has been demonstrated that the Doppler screening test is quick and reliable, and with less than 1% failures to obtain readings it does not have to be repeated (Bewley *et al.* 1989). An obstetric risk score, which could be calculated by computer, might be simple, but a 'roll over' test is more cumbersome. A screening test has to be easy, cheap, convenient, quick and non-invasive to be useful in clinical practice. Although the Doppler test fulfils these criteria, its accuracy would have to be improved first.

Screening the uteroplacental circulation of the general population at 16–24 weeks gestation will identify a group of women at high risk of developing serious complications. For the development of prophylactic treatments, this test, with a high cut-off, can be recommended. The risk of an individual developing a complication is increased by up to 9.8 times. The majority of patients with the complication will be missed or, if the cut-off is reduced it is at a cost of a high false positive rate. It remains to be determined if this false positive rate can be reduced by a modification of the technique or a simple second line investigation.

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Thyrotrophin-releasing hormone—a lactation-promoting agent?

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Abstract

Objective—To study the lactational and hormonal responses to nasal administration of thyrotrophin-releasing hormone (TRH) in puerperal women with inadequate lactation.

Design—Prospective randomized double-blind placebo-controlled study.

Subjects—19 puerperal women with inadequate lactation (<50% of normal milk yield) on the 5th day postpartum.

Interventions—10 women were allocated to receive TRH administered by a nasal spray of 1 mg, four times daily, between suckling episodes, for 10 consecutive days starting on day 6 postpartum. Nine women were allocated to receive placebo sprays.

Main outcome measures—Daily milk yield, serum levels of prolactin and thyroid hormones.

Results—Before treatment all the women had significant prolactin responses to TRH and suckling stimuli. At the end of 10 days of treatment, milk yield increased significantly in the TRH group from a mean of 142.0 (SD 33.9) to 253.0 (SD 105.3) g/day ($P = 0.014$). There was no significant change in the placebo group. Basal prolactin levels increased from a mean of 117.4 $\mu\text{g/l}$ (SD 45.2) to 173.3 $\mu\text{g/l}$ (SD 55.5) ($P < 0.001$) in the TRH group whereas in the placebo group prolactin levels decreased from 137.2 (SD 69.5) to 82.0 (SD 37.7) $\mu\text{g/l}$. A further rise in prolactin levels and milk yield was seen in seven women in the TRH group who received a second 10-day course of TRH treatment at their own request. There was no significant change in levels of thyroid stimulating hormone, thyroxine and triiodothyronine during treatment in either of the two treatment groups and no signs of hyperthyroidism.

Conclusion—Repeated nasal TRH administration between suckling episodes may improve defective lactation.

It is well established that prolactin is essential for the function of the mammary gland. Dopamine

antagonists in the early postpartum period have been shown to increase milk yield (Aono *et al.* 1979) and to improve defective lactation by elevating prolactin levels (Aono *et al.* 1982; Guzmán *et al.* 1979; Kauppila *et al.* 1981). Thyrotrophin-releasing hormone (TRH) has been given orally with the same intention (Tyson *et al.* 1976; Zárate *et al.* 1976; Ylikorkala *et al.* 1980). However, TRH was shown to be ineffective in further increasing fully established lactation. Results from the treatment of defective lactation are contradictory. Both Zárate *et al.* (1976) and Ylikorkala *et al.* (1980) were unable to demonstrate any effect of oral TRH on milk

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yield, but Tyson *et al.* (1976) observed complete correction of defective lactation. However, the treatment induced hyperthyroidism in some of these women. These divergent results may be a consequence of different selection criteria and study design. In an open pilot study, we demonstrated improvement of defective lactation after subcutaneous injections of TRH between episodes of breast feeding (Peters & Breckwoldt, 1979). In some species, TRH exerts a lactopoietic action (Wung *et al.* 1977) and the prolonged administration of TRH can induce galactorrhoea in non-pregnant women (Rabello *et al.* 1974). Consequently the new nasal preparation of TRH seems to afford an interesting opportunity to re-assess its effect on lactation in the human. Whereas recent studies did not involve a specified time schedule, the aim of the present study was to increase the number of prolactin peaks during the early lactation period. The effect of repeated application of TRH on milk production and the long-term usefulness in the treatment of inadequate lactation was investigated. Since it was suspected that in some women defective lactation may result from prolactin deficiency (Zárate *et al.* 1976; Kauppila *et al.* 1987), each woman had her prolactin response to the suckling stimulus and also her response to TRH assessed.

We also studied the endocrinological effects of the long term administration of TRH on baseline levels of prolactin, thyroid stimulating hormone (TSH), thyroxine (T_4) and triiodothyronine (T_3) in puerperal women.

Subjects and methods

All women delivered in our units, during 1986 at Freiburg and during 1987 at Mainz, received encouragement and advice on breast feeding from the nursing staff from the first post partum day onward. Primiparous women who had not achieved sufficient lactation by the 5th post partum day were informed of this double-blind study. To enter the study, milk yield had to be at least 50% less than the estimate of normal breast milk yield (165 mg/kg/day) (Editorial 1954).

The treatment order was pre-randomized by the pharmacist who prepared 20 spray vials, 10 of TRH solution and 10 of placebo (0.9% sodium chloride solution). These were of identical appearance. The vials were arbitrarily numbered from 1 to 20 and the code was known neither by the doctor nor by the women. The

women were consecutively allocated to the numbers of the randomization plan. The code was broken for analysis of the results only when all treatments had been completed.

Nineteen primiparous women agreed to participate in the study. Each woman had had an uneventful pregnancy and an uncomplicated spontaneous delivery at term. None of the women was taking any medication known to inhibit serum prolactin or puerperal lactation. None of the women or the babies had any illness. Ten women (mean age 26.2 years, range 19–35) received TRH by a nasal spray for 10 consecutive days starting on day 6 post partum. The dose of one spray consisted of 1 mg TRH. Nine women (mean age 23.5 years, range 17–34 years) received the placebo spray. The nasal spray was used four times daily between two suckling episodes and approximately 90–120 min after the last breast feed. All women were followed for a further 10 days (days 16–25 post partum). Thereafter, seven women from the TRH group requested a further treatment with TRH. They were then treated for a further 10 days using the same schedule (days 26 to 35 post partum). The infants were breast-fed on demand. Time intervals between suckling episodes ranged from 2 to 4.5 h. Daily milk yield was estimated by weighing the baby before and after each feed. The mean birthweight of the babies were 3489 g, (range 2950–4100 g) in the TRH group and 3139 g (range 2920–3960 g) in the placebo group.

According to the Declaration of Helsinki, each woman was fully informed about this placebo-controlled study and gave their consent freely. The TRH solution was generously donated by Hoechst AG, Frankfurt/Main, FRG.

Prolactin responses to suckling were tested in each of the 19 women directly before treatment and, to nasal TRH, during the first treatment application. Basal prolactin values and maximum responses were assessed from blood specimens drawn via an indwelling catheter every 10 min for 60 min.

Prolactin, TSH, T_4 and T_3 were determined before, during, and after treatment. Blood was drawn for hormone analysis, after an overnight fast, at about 0800 hours, before breast-feeding, approximately 8–10 h after the last nasal spray treatment. Prolactin, TSH, T_4 and T_3 radioimmunoassay kits were purchased from CEA-IRE-SORIN (Isotopendienst West, Dreieich-Frankfurt/Main). Methods have been described

previously (Peters *et al.* 1981). Statistical analysis included the *F*-test as a test of the homogeneity of variances, and the *t*-tests for paired and unpaired data were applied. Data were expressed as mean (SD) values.

Results

Clinical effects

All 19 women completed the study. At the end of 10 days of treatment, milk production in the TRH group had increased significantly from a mean of 142.0 g/day (SD 33.9) to 253.0 g/day (SD 105.3) ($t = 3.03$, $P = 0.014$), whereas in the placebo group milk production showed a small non-significant decrease from 150.0 g/day (SD 46.2) to 140.6 g/day (SD 57.7) ($t = 0.17$), $P = 0.87$).

After the end of treatment milk production remained unchanged in both treatment groups. At 5 days after the end of treatment (day 20 post partum), the values were 239.0 g/day (SD 123.3) in the TRH group and 146.7 g/day (SD 52.2) in the placebo group. At 10 days after the end of treatment (day 25 post partum), the values were 254.4 g/day (SD 121.9) in TRH group and 161.1 g/day (SD 60.3) in the placebo group (Fig. 1).

The seven women in the TRH group who were then treated with TRH for another 10 days showed a further increase in milk yield up to 424.3 g/day (SD 168.1). These women were able to breast feed without supplementation.

Nasal TRH applications were well tolerated by all the women. Occasionally, a brief attack of sweating was reported as a side effect. No clinical signs of hyperthyroidism were noted.

Hormonal results

Nasal administration of 1 mg of TRH resulted in significant prolactin responses within 30 min, from a mean value of 124.3 (SD 52.0) $\mu\text{g/l}$ to 262.0 (SD 80.4) $\mu\text{g/l}$ ($P < 0.0001$). The suckling stimulus induced a rise of prolactin from 129.5 (SD 57.7) $\mu\text{g/l}$ to 212.3 (SD 68.4) $\mu\text{g/l}$ ($P < 0.0001$). There was no statistically significant difference in the prolactin response either to suckling or TRH stimulation between the TRH and placebo group. Consequently, the prolactin stimulation responses of the two groups were analysed together. The prolactin responses to TRH and to suckling differed significantly ($t = 2.44$, $P = 0.02$) (Fig. 2). None of the women

had a blunted prolactin response. Regular nasal TRH treatment resulted in an increase of baseline prolactin levels from 117.4 (SD 45.2) $\mu\text{g/l}$ one day before treatment to 173.3 (SD 55.5) $\mu\text{g/l}$ on the 10th day of treatment ($t = -7.03$, $P < 0.001$, Fig. 1). This was significantly higher than in the placebo-treated group in which prolactin levels declined from 137.2 (SD 69.5) $\mu\text{g/l}$ to 82.0 (SD 37.7) $\mu\text{g/l}$ ($t = 3.04$, $P = 0.016$).

TSH, T_4 and T_3 serum levels were not significantly different between the two treatment groups during treatment, but on the 10th day of treatment and 5 days after treatment stopped, T_3 levels were significantly higher in the TRH group ($P < 0.01$) (Table I).

Discussion

Our results show that treatment with nasal TRH for 10 days improves milk yield by increasing the basal prolactin levels, but does not induce hyperthyroidism. Defective lactation has been shown to improve after stimulation of serum prolactin levels using sulpirid (Aono *et al.* 1982) or metoclopramide (Guzmán *et al.* 1979; Kauppila *et al.* 1981). The treatment of inadequate lactation by repeated oral TRH has yielded contradictory results (Tyson *et al.* 1976; Zárate *et al.* 1976; Ylikorkala *et al.* 1980; Canales *et al.* 1977). These divergent findings may be due to differences in study design or the use of different selection criteria. Zárate *et al.* (1976) treated their women with 20 mg TRH three times a day orally directly before breast feeding starting 2 weeks after delivery. Despite increasing basal prolactin levels, neither normal nor poor milk yield was augmented. The women described by Ylikorkala *et al.* (1980) received 20 mg TRH orally twice a day 3–10 weeks post partum when milk yield was insufficient and associated with significantly depressed prolactin levels. Tyson *et al.* (1976) treated 13 women with lactational insufficiency. Four received 5 mg TRH orally and nine received 20 mg twice a day each for 5 days. Treatment started between 13–71 days post partum. Full breast-feeding could be restored. However, the study was not placebo-controlled. Canales *et al.* (1977) found that lactation could be promoted using oral TRH four times a day.

In the present study, TRH and the suckling stimulus provoked similar prolactin surges. The suckling stimulus is essential for successful lactation, as demonstrated by Stewart & Pratt (1941). Furthermore, frequency of breast feed-

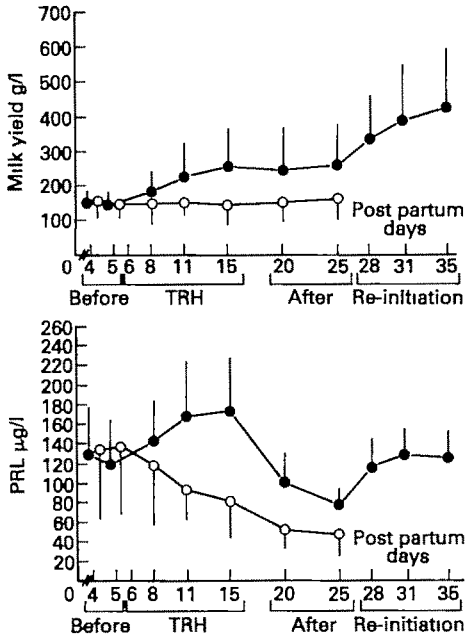


Fig. 1. Mean values and standard deviations of milk yield (upper panel) and serum prolactin (PRL) levels (lower panel) in two groups of puerperal women before, during and after treatment with (●—●) thyrotrophin releasing hormone (TRH) ($n = 10$) or (○—○) placebo ($n = 9$). Treatment by nasal spray started on day 6 post partum and continued for 10 days. Seven women received a second 10-day course of TRH (re-initiation) starting on day 27 postpartum. (See text for statistical data.)

ing is positively correlated with basal prolactin levels and the amount of milk production (Hennart *et al.* 1981). But some babies cannot be put to the breast as often as is theoretically desirable to increase prolactin levels and the present study was designed to induce more frequent prolactin bursts than would be possible with normal or even with increased number of suckling episodes. Repeated TRH application between suckling episodes stimulates additional prolactin output mimicking the endocrine features of normal breast feeding. Although serum prolactin levels do not correlate directly with milk yield (Howie *et al.* 1980), a dose-response correlation with drugs that influence prolactin has been demonstrated. Dopamine agonists inhibit and dopamine antagonists promote lactation gradually by varying serum prolactin levels (Peters *et al.* 1985; Kauppila *et al.* 1981). Furthermore, the number of suckling episodes has a similar effect. Decreasing suckling frequency results in falling prolactin levels and in reduced milk production (Hennart *et al.* 1981).

The new nasal preparation of TRH (1 mg per spray) that we used elicited a more rapid and higher prolactin output than a single 40 mg oral dose (Schurr *et al.* 1985). However, as TRH stimulates prolactin release to a lesser degree than is induced by dopamine antagonists (Sowers *et al.* 1976), TRH should be administered more than twice a day.

It seems reasonable to start treatment in the early puerperium since the therapeutic effects are poor in the late puerperium. Barguno *et al.* (1988) demonstrated that stimulated prolactin secretion may transiently increase milk production and improve infant weight gain only up to 30 days post partum.

The causes of lactation inadequacy are manifold. Functional disturbances such as anxiety of the mother, painful breasts or nipples or difficulties with the breast-feeding technique are thought to be important (Barnes *et al.* 1953). In these situations, insufficient milk yield may result from an impaired oxytocin reflex, so that there is an insufficient emptying of the breast. The oxytocin action is known to be inhibited by adrenalin (Vorherr, 1971), which may be released by stress or pain. Additionally, endorphins are known to inhibit oxytocin release in animal experiments (Clarke *et al.* 1979). The possible influence of an impaired oxytocin reflex was controlled in this study by offering a similar level of support to the lactating mothers in both groups.

Prolactin deficiency as a cause of defective lactation seems to be unusual, since all women in

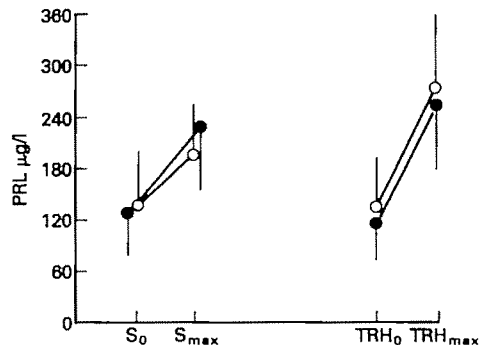


Fig. 2. Baseline prolactin (PRL) and maximum stimulation response to suckling (S) and thyrotrophin releasing hormone (TRH) in two groups of puerperal women. There was no significant difference in prolactin stimulation response between the (●—●) TRH and the (○—○) placebo groups. The maximum prolactin response to TRH was significantly greater than the response to suckling ($P = 0.025$).

Table 1. Thyroid hormone levels in puerperal women before, during and after treatment with thyrotrophin releasing hormone (TRH) or a placebo

Thyroid hormone	Before treatment	day 3	During treatment day 6	day 10	5 days after end of treatment
TRH group (n = 10)					
TSH (mU/l)	3.19 (1.3)	3.68 (1.5)	3.43 (1.26)	3.45 (1.18)	2.85 (1.09)
T ₄ (nmol/l)	102.7 (15.0)	105.8 (17.3)	117.7 (31.5)	123.9 (27.7)	109.9 (20.7)
T ₃ (nmol/l)	1.92 (0.32)	1.86 (0.52)	2.15 (0.6)	2.23* (0.23)	1.86* (0.3)
Placebo group (n = 9)					
TSH (mU/l)	3.2 (1.24)	3.1 (1.15)	3.17 (0.87)	3.08 (0.92)	3.11 (1.09)
T ₄ (nmol/l)	109.3 (16.7)	105.2 (17.5)	111.6 (21.2)	117.5 (14.6)	121.5 (13.7)
T ₃ (nmol/l)	1.8 (0.33)	1.73 (0.28)	1.83 (0.34)	1.72 (0.43)	1.71 (0.44)

*P<0.01 TRH vs placebo

Results are mean (SD) values

this study exhibited normal prolactin secretion. Kauppila *et al.* (1987) described such a defect in a parturient women with otherwise normal pituitary function presenting with alactogenesis. Zárate *et al.* (1976) described eight women with insufficient lactation due to a poor prolactin stimulation response to TRH. Although we found significant prolactin stimulation responses in all our subjects, it could be argued that a relative prolactin deficiency is part of the pathogenesis of poor lactation and that this may be compensated for by exogenous TRH stimulation. Since serum prolactin levels regulate the number of prolactin receptors in breast tissue (Bohnet *et al.* 1977), clinical effects are probably mediated by an increase in the number of prolactin mammary gland receptors. Furthermore, a newly detected factor, produced under the influence of prolactin by the liver in lactating rats, is a potent stimulator of lactation (Hoeffler & Frawley 1987) and may also be involved.

We have shown that nasal administration of TRH for 10 days in normal puerperal women increases serum prolactin to a greater extent than serum TSH. In contrast to the significant rise in prolactin, the increase in TSH, T₄ and T₃ was not statistically significant. The results obtained in the puerperium agree with findings in non-puerperal women (Rabello *et al.* 1974). A blunted TSH response to short term TRH may prevent changes in T₄ and T₃. Hyperthyroidism has been described as a serious side effect of long term high dose (40 mg) oral TRH administration (Tyson *et al.* 1976), but this was not observed in our patients.

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The effect of maternal anaemia and iron deficiency on the ratio of fetal weight to placental weight

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Abstract

Objective—To examine the maternal influences which determine large placental weight and a high ratio of placental weight to birthweight. These are known predictors of adult blood pressure.

Design—Retrospective analysis of routine obstetric and haematology department records for a large cohort of pregnant women.

Setting—John Radcliffe Hospital, Oxford.

Subjects—8684 pregnant women who were delivered between January 1987 and January 1989 and whose records could be linked to the results of two or more pregnancy blood counts

Main outcome measures—Placental weight and the ratio of placental weight to birthweight.

Results—Large placental weight was associated with a low maternal haemoglobin and a fall in maternal mean cell volume during pregnancy. The highest ratio of placental weight to birthweight occurred in the most anaemic women with the largest falls in mean cell volume. Large placental weight and a high ratio of placental weight to birthweight were also independently associated with a high maternal body mass index. Maternal smoking reduced placental weight, but increased the ratio of placental weight to birthweight.

Conclusions—Anaemia and iron deficiency during pregnancy are associated with large placental weight and a high ratio of placental weight to birthweight. This points to maternal nutritional deficiency as a cause for discordance between placental and fetal growth. This may have important implications for the prevention of adult hypertension, which appears to have its origin in fetal life.

High blood pressure in adult life is linked to lower birthweight (Barker *et al.* 1989; Barker *et al.* 1990). In a recent follow-up study of 449 men and women aged around 50 years who were born

in Preston, Lancashire the highest systolic and diastolic blood pressures occurred in people with heavy placentas and whose birthweight was lower than might be expected from their placental weight (Barker *et al.* 1990). These relations between measurements at birth and adult blood pressure were independent of current body mass index and alcohol intake.

Birthweight below that expected from placental weight was not limited to babies with low birthweight as currently defined. Most of the babies who failed to match their placental weight were of around the average birthweight but had a larger than average placenta. The maternal influences which lead to this discordance between fetal and placental weight and hence

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high blood pressure are unknown. Impaired nutrition and smoking are two possibilities.

We have therefore analysed antenatal data recorded routinely for 8684 women attending a maternity hospital in Oxford. Maternal dietary intakes are not of course measured during routine antenatal care. Haemoglobin and other red cell indices, however, are established indicators of nutrition (Medical Research Council 1945). The Oxford record linkage system allows haematology files to be linked directly to birth outcomes.

Subjects and methods

Between January 1987 and January 1989 there were 12 929 deliveries of liveborn singleton babies at the John Radcliffe Hospital, Oxford whose antenatal care had been in Oxford. The Oxford record linkage system enabled the obstetric data for 11 312 of these pregnancies to be linked to the results of full blood counts taken during the pregnancy. Failure to link the remainder largely resulted from a switch during the study period from unit number allocation by the maternity hospital to unit number allocation by the district. We limited our analysis to the 8684 pregnancies with two or more blood counts.

The obstetric data included maternal age, parity, height, weight at booking and at the last antenatal visit before delivery, smoking habits, first and maximum blood pressure, proteinuria, gestational age at delivery (estimated from the last menstrual period and ultrasound scan), infant sex, birthweight, placental weight and head circumference. Untrimmed placentas were weighed immediately after delivery. Complete data were available for 7903 pregnancies. Data on social class (coded by head of household's occupation) were available for 7423 of them.

Blood counts were determined on Technicon H6000 and Coulter S Plus 4 analysers using standard automated techniques. Changes in mean cell volume during the pregnancy were assessed by comparison with the mean cell volume at booking. Maternal body mass index, calculated as weight/height², was determined only for women whose first recorded weight measurement was before 20 weeks gestation. Discordance between birthweight and placental weight was assessed by determining the placental ratio (Heath & Williams 1990), calculated as placental weight/birthweight, and by adjusting the placental weight for the birthweight. These

indices gave similar results, so we present those for the placental ratio. The simultaneous trends in placental weight and in placental ratio with the lowest maternal haemoglobin and fall in mean cell volume were analysed by multiple regression.

Results

Both the lowest maternal haemoglobin during pregnancy and the fall in mean cell volume were independently related to increased placental weight. In Table 1 the divisions of maternal haemoglobin are based on the definition given by the World Health Organisation (1968) of pregnancy anaemia as a haemoglobin of <11.0 g/dl and on a commonly used clinical definition of 10.0 g/dl (Beischer *et al.* 1970). A fall in mean cell volume is probably the most sensitive indicator of iron deficiency determinable from serial routine full blood count measurements (Taylor 1981). At each level of haemoglobin, mean placental weight increased with falling mean cell volume. The increase in mean placental weight associated with a fall in mean cell volume greater than 6 fl ranged between 31 and 56 g at different haemoglobin levels. Likewise, at each level of fall in mean cell volume, placental weight rose as haemoglobin fell. Therefore, the highest mean placental weights occurred in women with a low haemoglobin and a large fall in mean cell volume, and the lowest weights occurred in women with a high haemoglobin and little or no fall in mean cell volume. The associations between placental weight and both minimum haemoglobin and fall in mean cell volume were statistically highly significant ($P < 0.0001$).

As expected lowest haemoglobin values and the fall in mean cell volume were associated. A fall in mean cell volume of >4 fl occurred in 43, 29, 16 and 9% of women whose lowest haemoglobins were <10.0, 10.0–10.9, 11.0–11.9 and ≥ 12.0 g/dl respectively.

Birthweight increased with lower maternal haemoglobin and with larger fall in mean cell volume (Table 2). The differences, however, were proportionally smaller than those with placental weight (Table 1).

Because placental weights approach term values at an earlier stage of gestation than do birthweights, it follows that the ratio of placental weight to birthweight increases with increasing degree of fetal immaturity. In turn, and consis-

Table 1. Mean placental weights (in grams) according to lowest maternal haemoglobin during pregnancy and fall in mean cell volume (The number of subjects is given in parentheses)

Lowest haemoglobin (g/dl)	Fall in mean cell volume (fl)			
	≤4	4-6	>6	All
≤ 9.9	634 (485)	673 (95)	672 (270)	650 (850)
10.0-10.9	622 (1777)	629 (331)	653 (392)	628 (2500)
11.0-11.9	605 (2841)	617 (312)	639 (222)	608 (3375)
≥12.0	583 (1780)	594 (129)	639 (50)	585 (1959)
All	606 (6883)	624 (867)	654 (934)	613* (8684)

*SD = 129 g.

tent with previous findings (Kaltreider & Kohl 1980), low maternal haemoglobin was associated with preterm delivery. In view of this we analysed the placental ratio only for babies born after 38 completed weeks (266 days) gestation estimated from the last menstrual period or an ultrasound scan before 20 weeks gestation (Table 3). Overall, there were independent statistically significant trends towards increasing placental ratios in association with lower maternal haemoglobin ($P < 0.0001$) and with larger falls in mean cell volume ($P < 0.0001$). Therefore, the highest placental ratios occurred in the most anaemic women with the largest falls in mean cell volume, and the lowest ratios in women with a high haemoglobin and little or no fall in mean cell volume.

Table 4 shows the percentage distribution of lowest haemoglobin values for women in each of three social class groupings: 41% of women in social classes IV and V had a haemoglobin below 11.0 g/dl, compared with 33% of women in social classes I and II (difference 8%, 95% confidence intervals (CI) 5-11%). Likewise, 23% of women in social classes IV and V experienced a fall in mean cell volume of >4 fl, compared with

19% of women in social classes I and II (difference 4%, 95% CI 2-7%).

We used multiple regression analysis to analyse the simultaneous relations of maternal haemoglobin, fall in mean cell volume, smoking habits and physique with the placental ratio for babies born after 38 weeks of gestation (Table 5). The placental ratio in each group is given as the difference from that of the baseline group. The size of the trends in placental ratio with lowest haemoglobin and fall in mean cell volume shown in Table 3 was only slightly changed by adjustment for the other variables. Inclusion of gestational age at delivery in the regression equation confirmed that these associations were independent of the length of gestation. Maternal smoking was associated with a small reduction in placental weight and a larger reduction in birthweight and therefore with an increase in placental ratio. Women with the highest body mass index had a mean placental ratio 0.0069 higher than those with the lowest body mass index as a consequence of an increase in placental weight that was not matched by the smaller increase in birthweight. In contrast to the findings for body mass index, the increase in

Table 2. Mean birthweights (in grams) according to lowest maternal haemoglobin during pregnancy and fall in mean cell volume. (Number of subjects is given in parentheses)

Lowest haemoglobin (g/dl)	Fall in mean cell volume (fl)			
	≤4	4-6	>6	All
≤ 9.9	3384 (485)	3536 (95)	3483 (270)	3432 (850)
10.0-10.9	3353 (1777)	3404 (331)	3481 (392)	3380 (2500)
11.0-11.9	3333 (2841)	3388 (312)	3454 (222)	3346 (3375)
≥12.0	3232 (1780)	3252 (129)	3428 (50)	3238 (1959)
All	3315 (6883)	3390 (867)	3472 (934)	3340* (8684)

*SD = 545 g.

Table 3. Mean ratio of placental weight to birthweight (placental ratio) according to lowest maternal haemoglobin during pregnancy and fall in mean cell volume for babies born after 265 days gestation. (Number of subjects is given in parentheses)

Lowest haemoglobin (g/dl)	Fall in mean cell volume (fl)			
	≤4	4-6	>6	All
≤ 9.9	0.185 (436)	0.188 (84)	0.192 (254)	0.188 (774)
-10.9	0.184 (1642)	0.184 (311)	0.187 (369)	0.185 (2322)
-11.9	0.180 (2623)	0.181 (291)	0.184 (210)	0.181 (3124)
≥12.0	0.179 (1596)	0.182 (115)	0.186 (47)	0.179 (1758)
All	0.181 (6297)	0.183 (801)	0.187 (880)	0.182* (7978)

*SD = 0.028.

placental weight associated with tall maternal stature was fully matched by a similar increase in birthweight, such that there was no significant relation between maternal stature and the placental ratio (data not shown).

Further analysis showed no significant associations between the placental ratio and maternal age, parity, blood pressure and proteinuria.

Discussion

We have shown that large placental weight and a high placental ratio, both known predictors of higher adult blood pressure (Barker *et al.* 1990), are related to low maternal haemoglobin and to a fall in mean cell volume.

This series of pregnant women came from the total population of women who had antenatal and intrapartum care over 2 years in the maternity hospital in Oxford. They were selected only by their obstetric records being linked with two or more full blood count results taken during the pregnancy. The mean placental ratio for pregnancies that were not linked to two or more blood count results was similar to that for pregnancies that were linked, 0.186 compared with

0.185. The mean haemoglobin in the first half of pregnancy was 12.3 g/dl for both the study population and for pregnancies excluded because they had less than two blood counts.

Maternal smoking and body mass index were also significantly associated with the placental ratio, but the relations with low maternal haemoglobin and the fall in mean cell volume were independent of these variables. In a study of 4-year-old children in Salisbury, blood pressure was related to maternal anaemia and low mean cell volume, but not to maternal smoking and body mass index (Law *et al.* 1991). The relation of pregnancy anaemia and low mean cell volume with blood pressure at 4 years of age suggests that factors influencing haemoglobin synthesis during pregnancy may be associated not only with discordance between placental weight and birthweight, but also with adult hypertension.

Severe maternal anaemia is known to be associated with large placental weight (Beischer *et al.* 1970). The dilutional fall in maternal haemoglobin during pregnancy due to a disproportionate increase in plasma volume may be thought of as reflecting good placental function, and thus likely to be associated with larger placental

Table 4. Percentage distribution of lowest haemoglobin during pregnancy by social class (Number of subjects is given in parentheses.)

Lowest haemoglobin (g/dl)	Social class			
	I and II	III	IV and V	All
≤ 9.9	7 (209)	10 (317)	12 (151)	9 (677)
-10.9	26 (757)	30 (964)	29 (372)	28 (2093)
-11.9	42 (1230)	38 (1200)	39 (496)	39 (2926)
≥12.0	26 (754)	22 (704)	21 (269)	23 (1727)
All	100 (2950)	100 (3185)	100 (1288)	100 (7423)

Table 5. Multiple regression analysis of the ratio of placental weight to birthweight (placental ratio) (95% confidence interval) associated with maternal lowest haemoglobin, fall in mean cell volume, smoking habits and body mass index for babies born after 265 days gestation

	Number of subjects	Increase in placental ratio relative to baseline group ($\times 10^{-3}$)
Lowest haemoglobin (g/dl)		
≤ 9.9	706	7.0 (4.4 – 9.5)
–10.9	2130	4.2 (2.3 – 6.0)
–11.9	2833	1.2 (–0.5 – 2.9)
≥12.0	1590	0
Fall in mean cell volume (fl)		
≤4	5717	0
4–6	729	0.8 (–1.4 – 2.9)
>6	813	4.4 (2.3 – 6.5)
Cigarettes smoked/day during pregnancy		
0	5725	0
1–10	814	8.8 (6.8 – 10.8)
≥11	720	9.4 (7.2 – 11.5)
Maternal body mass index (kg/m ²)*		
≤21.5	1295	0
–23.5	1447	3.2 (1.2 – 5.3)
–26.0	1293	3.5 (1.4 – 5.6)
≥26.0	1354	6.9 (4.8 – 9.0)
Not determined	1870	4.6 (2.6 – 6.5)

Intercept = 0.174

* Maternal body mass index was not determined for women who booked after 20 weeks gestation

weight. However, in a study of normal pregnant women stainable bone marrow stores of iron were absent in all women with haemoglobin values below 10.4 g/dl (de Leeuw *et al.* 1966). In the same study, oral iron therapy from early pregnancy completely prevented the mid trimester fall in haemoglobin that is commonly seen. World Health Organization committees have concluded that pregnancy haemoglobin values below 11.0 g/dl should not be considered physiological (World Health Organization 1968), but rather as nutritional in origin (De Maeyer 1989). The association of low social class with lower minimum haemoglobin (Table 4) and higher falls in mean cell volume during pregnancy strengthens the argument that these variables reflect poor maternal nutrition.

The fall in mean cell volume associated with a high placental ratio contrasts with the usual small rise in mean cell volume in normal pregnancy (Chanarin 1977). It points to iron deficiency (Taylor 1981). A fall in mean cell volume of >4 fl occurred in 43% of the pregnancies with lowest haemoglobin levels <10.0 g/dl and in

29% of those with lowest haemoglobin levels between 10.0 and 10.9 g/dl.

There are several possible explanations for the association between iron deficiency and both large placental weight and high placental ratio. It is unlikely that a relatively larger placenta would itself lead to greater consumption of maternal iron stores because the total iron content of the placenta is so much smaller than that of the fetus (Widdowson 1981). Rather we suggest that the large placental weight and high placental ratio are a consequence of iron deficiency, which induces placental hypertrophy that is disproportionate to fetal size.

As yet we can only speculate on mechanisms linking maternal anaemia and iron deficiency with high blood pressure. One possible explanation is that placental hypertrophy leads to a fast fetal growth path. The most rapidly growing fetuses are then most susceptible to nutrient deficiency, leading to relative failure of somatic growth and abnormal blood vessel growth.

A haemoglobin below the World Health Organization definition of pregnancy anaemia

or a fall in mean cell volume greater than 4 fl occurred in 47% of our study population. This suggests that pregnancy-associated iron deficiency is still an extremely common condition in this country.

At present our view is that the importance of advice to pregnant women to follow a balanced healthy diet should be reinforced. A recent study showed that supplementation with vitamins and minerals including iron during pregnancy had no effect on birth dimensions when given during the last two trimesters of pregnancy. In contrast, there was a strong relation between birth dimensions and the recorded maternal intake of many nutrients in the first trimester (Doyle *et al.* 1990). More specific advice to pregnant women must await further studies.

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Fetal blood sampling and pregnancy loss in relation to indication

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Abstract

Objective—To assess the relation between the indication for fetal blood sampling and pregnancy loss following the procedure.

Design—Retrospective study

Setting—The tertiary referral Fetal Medicine Units at Guy's and University College Hospitals, London

Subjects—Women undergoing diagnostic fetal blood sampling in four groups: (1) 94 having prenatal diagnosis with normal ultrasound findings; (2) 94 with a structural fetal abnormality; (3) 30 having fetal assessment and (4) 35 with non-immune hydrops.

Interventions—Freehand ultrasound guided fetal blood sampling from umbilical cord, intrahepatic vein or fetal heart.

Main outcome measures—Pregnancy losses were divided into those within 2 weeks and those 2 weeks after the procedure, obstetric accidents and neonatal deaths

Results—The 253 patients had fetal blood sampled on 268 occasions. Fifty-one pregnancies were terminated. Overall, 51 of the remaining 202 desired continuing pregnancies were lost, of which 19 (9%) were lost within 2 weeks of the procedure. After exclusion of the pregnancies that were terminated, the procedure-related losses within 2 weeks of sampling were 1 in 76 (1%), 5 in 76 (7%), 4 in 29 (14%) and 9 in 36 (25%) in groups 1, 2, 3 and 4 respectively.

Conclusions—The risk of fetal blood sampling is increased in abnormal pregnancies, reflecting the underlying pathology and this must be taken into account when counselling patients before the procedure

Percutaneous ultrasound guided fetal blood sampling was introduced by Bang (1982). A rapid expansion of ultrasound guided needling techniques has followed, allowing a wide range of diagnostic and therapeutic applications. Indications for fetal blood sampling include the detec-

tion of inherited genetic diseases and the investigation of ultrasonically abnormal fetuses.

The risk of pregnancy loss associated with percutaneous umbilical blood sampling is estimated at 1-2% (Daffos *et al* 1985). Increased loss rates have been reported in 'high risk' pregnancies

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(Nicolaidis 1988; Nicolini *et al.* 1990) but procedure related loss has never been precisely defined. Most would agree that a loss within 24 h of an invasive procedure should be described as procedure related. The issue becomes more complicated with losses after this time, particularly when pregnancies complicated by structural, metabolic or karyotypic abnormality are considered; such cases have a high risk of intrauterine fetal death and miscarriage.

The aim of this retrospective analysis was to determine the number of pregnancies lost in association with ultrasound guided fetal blood sampling for common clinical indications.

Patients and methods

Between April 1987 and July 1990 a total of 268 fetal blood samplings were performed on 253 singleton pregnancies for reasons other than the management of rhesus immunization at either Guy's Hospital or University College Hospital, London. Initial samplings at both institutions were by one operator (D J.M.) The same technique has been continued at each centre, using identical ultrasound equipment (Acuson 128).

A preliminary ultrasound scan was performed with identification of the placental insertion of the cord using a 3.5 MHZ sector or linear transducer. The maternal abdomen was cleaned with antiseptic and 1% lignocaine skin infiltration given at the site of needle insertion. With the transducer held in one hand, a 22 gauge single use spinal needle was introduced freehand into the placental insertion of the umbilical cord under continuous ultrasound guidance, either directly through the placenta or transamniotically. Where the placental insertion could not be seen clearly, or when fetal lie made access impossible, the fetal insertion of the cord, a free loop of cord, the intrahepatic vein or the fetal heart were used as alternatives. The volume of blood aspirated was between 0.5 and 2 ml, depending upon gestational age and indication for sampling.

The pregnancies were divided into four groups: (1) prenatal diagnosis of genetic disorders; (2) investigation of fetuses with structural anomaly; (3) fetal assessment (e.g., acid base status), and (4) nonimmune hydrops.

Calculation of losses

Fifty-one pregnancies were terminated after the results of the fetal blood sampling became avail-

able, and these were subtracted from the total to establish the number of desired continuing pregnancies. None of the terminated pregnancies was complicated by bleeding or infection before the termination, most of which were done between 7 and 14 days after the blood sampling.

All other losses (intrauterine fetal deaths, miscarriages, neonatal deaths and obstetric accidents) were added together to give a total loss of desired pregnancies, with division into pregnancies lost within 2 weeks of the procedure, those lost more than 2 weeks after the procedure, obstetric accidents and neonatal deaths. We believe that pregnancies lost within 2 weeks of the procedure are likely to include those most directly attributable to the procedure.

Indications

The indications for fetal blood sampling in the four groups are shown in Table 1. For the purpose of this study, hydrops was defined as the presence of a fluid accumulation in more than one site within the fetal body, with or without polyhydramnios (Romero *et al.* 1988).

Results

There were 268 procedures of which ten were cardiac punctures, five were from the intrahepatic vein and all others were cord samples. There were 13 failed samplings and repeat procedures were not always performed, amniocentesis, chorion villus sampling or fetoscopic blood sampling being employed as alternatives in five pregnancies.

Figure 1 shows the gestations at which the samplings were performed. A summary of the outcome is shown in Table 2. Details of pregnancy losses are given in Table 3.

Details of pregnancy losses

Group 1 The single early loss in the prenatal diagnosis group was in a pregnancy in which there had been chorion villus sampling at 10 weeks for raised maternal age. This culture showed a mosaic (50% 46 XY, 50% 46 XYt (8,13) balanced) so amniocentesis was performed at 16 weeks to clarify the karyotype, 70% of these cells showed the mosaicism, and an uncomplicated fetal blood sampling was performed. Miscarriage occurred 1 week later, and histology confirmed chorioamnionitis. Another baby, born at term,

Table 1. Indications for fetal blood sampling

Group 1. Prenatal diagnosis		Group 2. Structural anomalies	
67	Haemoglobinopathies	28	Cardiac
10	Failed amniocentesis culture	16	Multiple
6	Clarify amniocentesis result	12	Renal
5	Fragile X	10	Diaphragmatic hernia
4	RMA, late booker	5	Pericardial effusion
3	AFP abnormalities	5	Head abnormality
1	Poor obstetric history	4	Exomphalos
		4	Tachyarrhythmia
		4	Intrathoracic mass
		3	Duodenal atresia
		1	Choroid plexus cysts
		1	Pleural effusion
Group 3 Fetal assessment		Group 4. Nonimmune hydrops	
10	IUGR	25	Nonimmune hydrops
9	IUGR + raised PI or AEDF	5	Tachyarrhythmia
5	Oligohydramnios (3 PPRM)	4	Structural heart disease
3	Infections	1	Congenital heart block
3	ITP		

Abbreviations RMA, raised maternal age, AFP, alphafetoprotein, IUGR, intrauterine growth retardation; PI, pulsatility index, AEDF, absent end diastolic flow, PPRM, preterm prelabour rupture of membranes; ITP, idiopathic thrombocytopenic purpura.

died in the neonatal period. This baby was thought to be structurally normal on ultrasound at the time of fetal blood sampling at 28 weeks, but postnatally was found to have total anomalous pulmonary venous drainage.

Group 2. In the structural anomalies group many of the fetuses had lethal structural or karyotypic abnormalities. The single pregnancy complicated by chorioamnionitis followed an uncomplicated procedure for karyotyping a fetus with an isolated pericardial effusion at 19 weeks. The karyotype was normal.

Group 3 In the assessment group, seven of the fetuses were found to be hypoxic and acidotic at the time of blood sampling. In view of the early onset of growth retardation and the profound hypoxia in two pregnancies, the obstetricians responsible decided that delivery was inappropriate, and both fetuses died *in utero*. A further pregnancy was interrupted because of fulminating pre-eclampsia at 24 weeks.

Group 4 There were more losses in the non-immune hydrops group. Two fetuses infected with parvovirus, who had severe anaemia and were hypoxic and acidotic, died *in utero*, within 2 weeks of the procedure. Of the remainder, four were both hypoxic and acidotic at the time of sampling, although no cause for the hydrops was detected after haematological, biochemical and virological investigation, and all four died within 2 weeks. No cause was found for the hydrops in any of the three fetuses who died more than 2 weeks after the procedure.

Complications

Complications occurred in few of our procedures. In nine pregnancies, repeat needle insertions were required, often secondary to fetal movement during the procedure. Transient

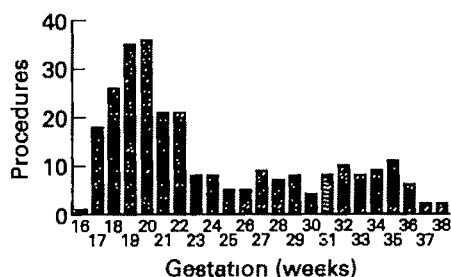


Fig. 1. Gestation at fetal blood sampling, 268 procedures in 253 pregnancies.

Table 2. Fetal blood sampling—total pregnancy losses

Group	1	2	3	4	Total
Total procedures	97	98	31	42	268
Total patients	94	94	30	35	253
Failed procedures	4	6	3	—	13
Repeat samples	3	4	1	7	15
Termination	21	22	2	6	51
Desired pregnancy	73	72	28	29	202
Obstetric accident	—	1	—	1	2
Loss within 2 weeks	1	5	4	9	19
Loss after 2 weeks	—	4	—	3	7
Neonatal death	1	14	2	6	23
Total losses	2	24	6	19	51
Losses within 2 weeks (percentage of desired ongoing pregnancies)*	1 (1.3)	5 (6.6)	4 (13.8)	9 (25)	19 (8.8)

*Percentage of desired ongoing pregnancies = $\frac{\text{Losses within 2 weeks}}{\text{Total procedures} - \text{Terminations}}$

bradycardias accompanied sampling on four occasions. One of these resulted in a pregnancy loss: this was a severely growth retarded fetus at 24 weeks with reversed end diastolic flow on umbilical Doppler blood flow studies in whom profound bradycardia accompanied the procedure and intrauterine fetal death was confirmed 48 h later. In one pregnancy maternal sedation was required. No babies were born as a result of a complication of fetal blood sampling, and no complications occurred in the samplings from the fetal heart or intrahepatic vein.

The differences in procedural loss between the four groups was highly significant ($\chi^2 = 18.535, 3$ d.f.) Further χ^2 -testing to look at the effect of gestation and group on procedural loss did not reveal statistically helpful information.

Discussion

Pregnant women for whom ultrasound guided fetal blood sampling could provide important information require informed counselling beforehand as to the likely risks and benefits of the procedure. The first large series of ultrasound guided fetal blood samplings was published by Daffos (1985). In that series, investigation for toxoplasmosis was the largest single indication, accounting for 413 of the 606 samplings. Of the remainder, 39 were for rapid karyotyping, but the precise indication was not given in the paper. It is therefore impossible to assess whether any high risk pregnancies were investigated. His estimated risk of pregnancy loss secondary to the

procedure was 2%. In a combined series of published and unpublished data, Weiner (1988) estimated the procedural loss at 0.15%. Although he mentioned the difficulty of assessing whether a loss in an abnormal pregnancy was procedure related or a reflection of the underlying pathology, he did not examine this further. In a study of the technical aspects of fetal blood sampling, Boulot *et al.* (1990) chose the limit of 15 days for losses directly related to the procedure. However, they did not provide full details of the indications for the procedure in these cases.

Smaller series have been published but without specific reference to the indication for sampling. Hobbins *et al.* (1985) reported 13 pregnancies. One neonatal death occurred as a consequence of preterm delivery. Weiner (1987) published a series of 96 cordocenteses, the main indication for which was the investigation of rhesus immunization. In that series there were no losses within 2 weeks, but one neonatal death and one obstetric accident. Both these babies had abnormal karyotypes. We have excluded pregnancies with Rhesus immunization as the repeated procedures required cannot be compared to other groups in this analysis.

Pielet *et al.* (1988) reported 27 pregnancies with two neonatal deaths, both babies were structurally abnormal and would fit into our group 2. This highlights the additional loss of desired continuing pregnancies in the presence of an abnormal fetus. Many other small series have been published (Kurjak *et al.* 1987; Scioscia *et al.* 1988; Hogge *et al.* 1988; Pardi *et al.* 1987). With

Table 3. Pregnancy losses—underlying pathology

Group 1. Prenatal diagnosis		Group 2. Structural anomalies	
<2 weeks		<2 weeks	
1	Chorioamnionitis	1	Chorioamnionitis
		1	Multiple abnormalities
		1	Oligohydramnios, renal abnormalities, AEDF
		1	Hydrocephalus
		1	47 + 18
>2 weeks		>2 weeks	
	nil	1	Cardiac mass
		1	69 XXX
		2	47 + 18
Obstetric accidents		Obstetric accidents	
	nil	1	47 + 2, fetal distress in labour, no CS
Neonatal death		Neonatal death	
1	Total anomalous pulmonary venous drainage	6	Structural heart disease
		4	Diaphragmatic hernia
		3	47 + 18
		1	47 + 13
Group 3. Fetal assessment		Group 4. Nonimmune hydrops	
<2 weeks		<2 weeks	
2	AEDF + IUGR (24 and 28 weeks)	4	Nonimmune hydrops
1	IUGR + severe PET (28 weeks)	2	Parvovirus
		2	SVT on flecainide
1	Severe IUGR (24 weeks)	1	Placental haemangioma
>2 weeks		>2 weeks	
	nil	3	Nonimmune hydrops
Obstetric accidents		Obstetric accidents	
	nil	1	Labour at 28 weeks fetal distress, no CS
Neonatal deaths		Neonatal death	
1	Severe IUGR	6	Nonimmune hydrops
1	Pulmonary hypoplasia		

Abbreviations: AEDF, absent end diastolic flow; IUGR, intrauterine growth retardation; CS, caesarean section; PET, pre-eclampsia; SVT, supraventricular tachycardia.

small numbers, it is difficult to assess risk in any diagnostic group. Anecdotal reports (Benacerraf *et al.* 1987; Feinkind *et al.* 1990) serve to underline the inherent risk in the procedure of fetal blood sampling, but do not help us with assessing the prospective risk.

The principal aim of the present analysis was to provide information that might be helpful in prospective counselling before fetal blood sampling during pregnancy. Although our analysis is retrospective, the classification of indications for the procedure was prospective, based on history and ultrasound findings. The highly significant difference in losses between the groups validates this classification. Where the indication for fetal

blood sampling was blood gas analysis the ability to deliver the distressed fetus introduces a bias and therefore any risk assessment at later gestations can only be an estimate. Our series does, however, contain a larger number of procedures at earlier gestations than was published previously.

We have combined the data from two institutions to achieve sufficient numbers for analysis. One of the operators has performed a substantial number of the procedures in both institutions and has been responsible for the training of the other operators in a standard technique using identical high resolution ultrasound systems.

The four groups of pregnancies studied are

representative of common clinical situations where information from a fetal blood sample would be helpful in obstetric management. There were no control groups in which no procedure was performed for comparison. Therefore, a precise procedure related risk cannot be established for any of the groups in the study. The large numbers of terminations would have included some pregnancies destined to miscarry. In the fetal assessment group, the clinician's freedom on whether or not to deliver a 'sick' hypoxic or acidotic fetus introduces further bias, irrespective of the decision made. This analysis confirms an inherent risk related to the procedure of ultrasound guided fetal blood sampling. In an uncomplicated pregnancy a realistic estimate is 1–2%. However, if a fetus is known to be structurally abnormal or is suspected of being metabolically abnormal, the pregnancy losses are higher. How much of the increased loss in the more complicated pregnancies is due to the procedure or to the natural history of the disease *in utero* remains uncertain. The time limit of 2 weeks following sampling to compare losses in each of our groups was arbitrary. It did, however, include all immediate losses and cases of chorioamnionitis. Loss rates for this portion of the analysis rose from 1.3% in the prenatal diagnosis group to 25% in the group with non-immune hydrops reflecting the severity of underlying clinical disease within the groups.

When pregnancy losses for sampling sites other than the umbilical cord are considered, only one occurred within 2 weeks after cardiac puncture in a severely anaemic, hypoxic and acidotic fetus with hydrops secondary to infection with parvovirus. Other workers have found little difference in procedure related loss when alternative sampling sites were employed (Nicolini *et al.* 1990; Nicolini *et al.* 1988).

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Mode of delivery and neonatal death in 17 587 infants presenting by the breech

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Abstract

Objective—To study the effects of caesarean section on neonatal mortality in infants presenting by the breech.

Design—Population-based non-experimental comparison of infants presenting by the breech born vaginally with those born by caesarean section. Neonatal mortality rates were calculated for 250 g birthweight intervals. Weight-specific relative risks (RRs) were further adjusted for birthweight in 50 g categories.

Setting—New York City, 1978-1983. Data came from the Department of Health's computerized vital records on livebirths and infant deaths.

Subjects—17 587 singleton breech livebirths ≥ 500 g birthweight, with congenital anomaly deaths excluded. 6178 were born vaginally and 11409 were born by caesarean section.

Main outcome measure—Birthweight-specific and birthweight-adjusted neonatal mortality.

Results—At birthweights of 501 to 1750 g, the risk of neonatal death for breech infants born vaginally was significantly higher than the risk for those born by caesarean section (weight-adjusted $RR=1.7$). For breech infants with birthweights over 3000 g, the weight-adjusted risk was 5.6 times greater for a vaginal birth compared with caesarean section. The addition of 16 additional control variables in multiple logistic regression analyses did not change these RRs.

Conclusion—Population-based studies indicate that an increase in the caesarean section rate among breech singletons may be associated with increased neonatal survival, but a large multicentre randomized trial of management of breech presentation would answer the question much more definitively.

This is a report of the results of an analysis of whether babies presenting by the breech who are born vaginally are at higher risk of neonatal mortality than those who are born by caesarean section. The data were non-experimental, that is, pregnant women were not randomly allocated to

vaginal or caesarean 'treatment' groups. In non-experimental studies of therapeutic interventions, selection bias can be a major problem (Chalmers 1983; Feinstein 1985; Miettinen 1983). In assessing perinatal interventions, where the decision to intervene is made by the clinician, selection bias operates as follows: women at different risks of an adverse outcome have different probabilities of receiving the intervention being studied (Greenland & Neutra 1980). In this case, a comparison of outcomes in caesarean and vaginal births is confounded by the fact that the two groups have different inherent risks (Lumley *et al.* 1985).

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The question of whether it is possible to carry out a valid nonrandomized comparison hinges on whether it is possible to get rid of selection bias through analytic techniques. It may be impossible to measure adequately all the confounding variables that could lead to selection bias—let alone control for them (Chalmers 1983). Nevertheless, since only two small randomized trials have compared outcomes in vaginal and caesarean delivery in breech presentations (Collea *et al.* 1980; Gimovsky *et al.* 1983), the obstetric community is forced to rely on non-experimental data for policy and decision-making (Bingham & Lilford 1987).

The evidence that the fetus presenting by the breech may already be damaged is compelling (Hyttén 1982; Confino *et al.* 1985; Collea 1981). Fetuses with a wide range of morphological and functional damage more commonly present by the breech (Brenner *et al.* 1974; Braun *et al.* 1975; Mazor *et al.* 1985). A clinician's perception that a fetus is malformed may influence the choice of mode of delivery; this is another factor that must be kept in mind in assessing the validity of non-experimental comparisons of mortality in vaginal and caesarean delivery. In the study reported here, deaths attributed to congenital anomaly were excluded.

With breech presentation, babies tend to be much lighter when born vaginally than when caesarean section is used (Tompkins 1946; Berendes *et al.* 1965; Brenner *et al.* 1974). Therefore, birthweight is the most important confounding variable that must be controlled when neonatal mortality is compared in the two groups. In past comparisons that have adjusted for birthweight (Rosen & Chik 1984; Petitti & Golditch 1984; Mann & Gallant 1979; Bowes *et al.* 1979; De Crespigny & Pepperell 1979), the unadjusted relative risk (RR) of neonatal mortality for vaginal vs caesarean delivery was much higher than the birthweight-adjusted RR. For example, in a study of mode of delivery in breech presentations reported by Rosen & Chik (1984), the unadjusted RR was 5.8, but this was reduced to 1.3 after adjustment for birthweight differences between the vaginal and caesarean groups. In the study reported here, the birthweight-specific effects of mode of delivery in breech presentation were examined.

Subjects and methods

The study population was derived from certified

vital records of livebirths and infant deaths in New York City. These records are entered into computer storage by the Department of Health. Data on neonatal deaths were taken from certificates of death in the first year, which are routinely linked to their matched birth certificates and jointly stored in a separate computer file. The six, yearly, livebirth files from 1978–83 and the seven, yearly, infant death files from 1978–84 were used to create a data set consisting of birth and death information on all liveborn babies born after breech presentation in New York City between 1 January 1978 and 31 December 1983. Multiple births, caesarean sections for women who had had a previous caesarean section, and all babies weighing ≤ 500 g were excluded from the analysis. Deaths attributed to congenital malformations (ICD-9 codes 740.0–759.9) were also excluded. There were 17 587 breech presentations in the analysis.

Stillbirths were excluded from the study. While the New York City Department of Health does maintain a separate computer file of fetal death certificates, among fetal deaths ≥ 24 weeks gestation 70% of the records indicate that death occurred before labour and 15% indicate that time of death was unknown. In the remaining 15%, that indicate that death took place during labour, it is uncertain whether the stillbirth occurred before the second stage of labour. Because of this uncertainty in the stillbirth data, it was decided that neonatal death would be the most appropriate mortality index.

The neonatal mortality rate was defined as the number of liveborn infants dying in the first 28 days per 1000 livebirths. Birthweight was used as the primary control variable rather than gestational age because of the questionable reliability of date of last menstrual period (LMP) recorded on birth certificates (David 1980, Kleinman 1991).

Data analysis

In order to inspect the extent of selection bias, an analysis was carried out of differences in birthweight distributions between breech presentations born by caesarean section and those born vaginally.

Neonatal mortality rates for vaginal and caesarean births were then calculated for 250 g birthweight intervals. RRs of neonatal mortality for vaginal compared with caesarean births were estimated. RRs are reported for 12 birthweight

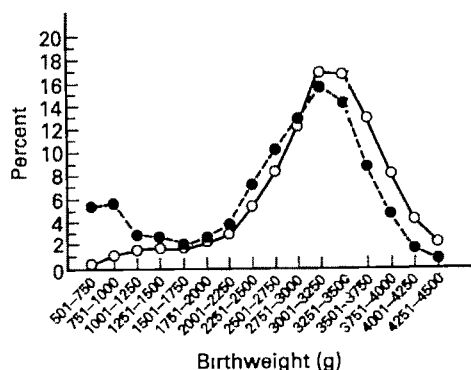


Fig. 1. Birthweight percentage distributions of breech presentations by mode of delivery, New York City, 1978-1983, —●— vaginal births; -○- caesarean sections

categories. In order to avoid residual confounding that could have resulted from the differences between the weight distributions of vaginal and caesarean births, the RR for each weight category was further adjusted for birthweight in 50g categories. These birthweight-adjusted RRs were estimated using the 'directly pooled' point estimation method suggested by Rothman (1986). Confidence limits were derived using an iterative Cornfield-Gart procedure (Fleiss 1981).

In additional multivariate analyses, birthweight, gestational age, and 15 other social, demographic, and biomedical variables were entered into maximum likelihood logistic regressions (Brand & Keirse 1990; Harrell 1986; Lee 1981). Gestational age was estimated by computing the number of days between the LMP and the date of birth.

Results

Birthweight distributions

Overall 64.5% of the women with breech presentations were delivered by caesarean section and 35.5% were delivered vaginally. The birthweight distributions in the two groups are shown in Fig. 1. Median birthweight was 288 g less after vaginal birth than after caesarean section (2892 g vs 3180 g) and mean birthweight was 464 g less (2634 g vs 3098 g). On examining the gaussian ('normal') part of the distribution (the part above 2000 g) it appears that the birthweight distribution of vaginal births is shifted 200-300 g to the left of the distribution for caesarean sections. However, the most striking feature in Fig. 1 is the high proportion of very-low-birthweight breech presentations born vaginally compared with those born by caesarean section. Overall, 1.5% of babies born by caesarean section weighed <1001 g, whereas 12.4% of those born vaginally weighed <1001 g, and 4.9% of babies born by caesarean section weighed <1501 g compared with 17.9% of those born vaginally. The percentages under 2001 g were 8.9 and 22.4 for the caesarean and vaginal groups, respectively, and the percentages under 2501 g were 17.9 and 33.1.

Neonatal mortality

Table 1 demonstrates the neonatal mortality rates in New York City breech presentations. Vaginal birth had a death rate more than seven times higher than the rate after birth by caesarean section. Of course the comparison of these two groups was confounded by the differences in their birthweight distributions. When adjusted for birthweight in 50 g intervals, the

Table 1. Singleton livebirths in breech presentation, * New York City 1978-1983. Neonatal mortality in vaginal delivery compared with caesarean section

Mode of delivery	Livebirths	Neonatal deaths	NMR†
Caesarean section	11 409	169	14.8
Vaginal delivery	6178	685	110.9

Unadjusted RR‡ = 7.49

Birthweight-adjusted RR = 1.64

95% Confidence interval = 1.44-1.86

*Excluding all those with birthweights under 501 g and infant deaths in which the underlying cause of death was a congenital anomaly.

†NMR indicates neonatal deaths per 1000 livebirths.

‡RR indicates relative risk with the caesarean group as the referent group

adjusted RR was 1.64, indicating that vaginal birth had a 64% excess risk of neonatal death compared with caesarean section when birthweight was controlled.

Figure 2 displays neonatal mortality per 1000 livebirths with breech presentation after vaginal delivery and caesarean section. Throughout most of the birthweight range, vaginal delivery was associated with a higher mortality rate than caesarean section. The only part of the birthweight range where the difference was not statistically significant was between 1751 and 3000 g.

Table 2 shows the RRs in each of 12 birthweight categories. The RRs represent the neonatal mortality rate after vaginal delivery divided by the rate after caesarean section. These RRs are adjusted for birthweight in 50 g categories. Between 500 and 1750 g, RRs ranged from 1.4 to 5.2. The adjusted RR for the birthweight range between 501 and 1750 g was 1.68 (95% confidence interval: 1.46–1.94).

The RRs between 1751 and 3000 g were not statistically significantly different from 1.00. The statistical power in this part of the birthweight range was not very high, since there were rela-

tively few deaths in these weight groups. Even though there were 5723 breech presentations that weighed 1751 to 3000 g, there were only 66 deaths in this weight range. The adjusted RR for the birthweight range between 1751 and 3000 g was 1.13 (95% confidence interval: 0.76–1.68).

Between 3001 and 3750 g, the RR was a remarkably high 4.3. Between 3751 and 4250 g, neonatal mortality was twice as high in the vaginal delivery group as in the caesarean group, but this was not statistically significant owing to the small number of deaths. Above 4250 g there were 8 deaths among 72 vaginal births and 0 deaths among 444 caesarean births; this difference is highly statistically significant (Fisher's exact test $P=1.01^{-7}$). The birthweight-adjusted RR for all births who weighed more than 3000 g was 5.64 (95% confidence intervals: 3.13–10.18).

After controlling for the variables in Table 3, using multivariate logistic regression analyses, the addition of 16 more variables did not change the RR from the 1.6 that was found when only birthweight was controlled. Also, when separate multivariate regression analyses were performed within each of the 12 birthweight strata shown in Table 2, none of the birthweight-specific adjusted RRs changed by more than 10%.

Discussion

These findings indicate that the risk of neonatal death for infants with breech presentation born vaginally was significantly greater than for those born by caesarean section. Since this research was based on vital records, it has certain shortcomings. First, the vaginal deliveries were not divided into different kinds of breech deliveries, such as assisted breech, spontaneous breech, and breech extraction. Second, the breech presentations were not classified into frank breeches, footling breeches, and so forth. This information is not available on the New York City birth certificate. Third, and perhaps most important, it was not possible to analyse the effect of mode of delivery on childhood morbidity or maternal morbidity. Fourth, data limitations made it necessary to compare vaginal delivery with caesarean section as a whole, without making a distinction between elective section and emergency sections performed for a failed trial of vaginal delivery. Ideally one should know the proportion of failed trials of vaginal breech delivery (Bingham & Lilford 1987). Fifth, some of the

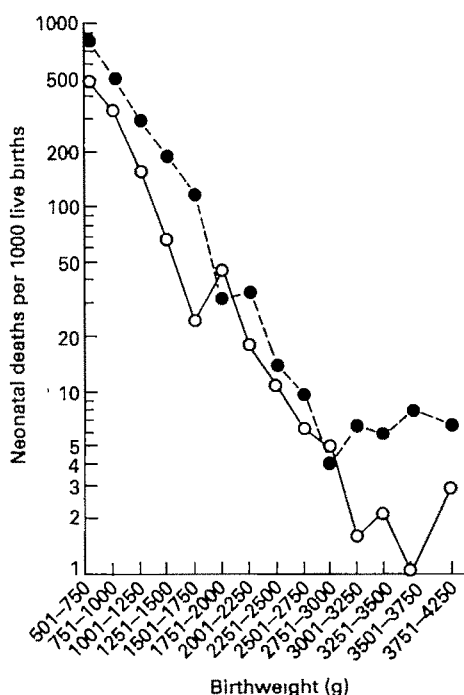


Fig. 2. Neonatal mortality in breech presentations by mode of delivery, New York City, 1978–1983. —●—●— vaginal births; —○—○— caesarean section.

Table 2. Singleton livebirths in breech presentation,* New York City, 1978–1983: relative risks for neonatal mortality in vaginal delivery compared to caesarean section, by birthweight

Birthweight (g)	Total livebirths	Total neonatal deaths	Birthweight-adjusted RR†	(95% CI)
501–750	364	280	1.64	(1.31–2.05)
751–1000	467	219	1.44	(1.13–1.83)
1001–1250	369	85	1.96	(1.29–2.97)
1251–1500	354	45	2.84	(1.60–5.06)
1501–1750	316	19	5.17	(1.99–13.44)
1751–2000	414	17	0.65	(0.21–2.05)
2001–2500	1509	27	1.57	(0.73–3.36)
2501–3000	3700	22	1.15	(0.48–2.73)
3001–3750	7575	23	4.27	(1.93–9.44)
3751–4250	1766	6	1.93	(0.35–10.47)
≥4251	516	8	—	—
Unknown weight	137	103	1.41	(0.82–2.44)
Total (all birthweights)	17 587	854	1.64	(1.44–1.86)

*Excluding infant deaths in which the underlying cause of death was a congenital anomaly

†RR indicates relative risk adjusted for birthweight in 50 g categories, caesarean group is referent group

variables that were controlled in multiple regression analyses (Table 3) may have been measured unreliably (Kleinman 1991; Carucci 1979). In particular, there is reason to be concerned that more precise measurement of gestational age, pregnancy complications, and complications of labour and delivery could have resulted in 'tighter' control of confounding and, therefore, smaller adjusted RRs.

Neonatal mortality rates were reported for birthweight categories rather than gestation categories, owing to the questionable reliability of LMP-based gestation data (David 1980; Kramer *et al.* 1988; Kleinman 1991). Differences in outcome by gestational age would have been more useful as a guide to obstetric practice, since it is difficult to accurately determine fetal weight prior to delivery. Future clinical studies of mode of delivery in breech presentation should attempt to collect reliable information on gestational age, preferably based on ultrasonographic scanning before 20 weeks gestation (Kramer *et al.* 1988).

This study was population-based and every effort was made to control for potentially confounding differences between vaginal deliveries and caesarean sections. Therefore, given the limited information available from randomized controlled trials of management of breech presentation (Colle *et al.* 1980; Gimovsky *et al.* 1983), the findings of this New York City study are among the best evidence available on this issue. In this population of fetuses with breech

presentation, the overall birthweight-adjusted risk of neonatal death was about 60% higher after vaginal delivery as opposed to caesarean section. For babies weighing less than 1751 g at birth, mortality was about 70% higher after vaginal delivery than after caesarean section. For infants with birthweights between 1751 and 3000 g, there was little difference in neonatal mortality between the vaginal and caesarean groups.

In babies weighing more than 3000 g at birth, mortality was more than five times higher after vaginal delivery than after caesarean section. This latter finding is in agreement with previous estimates of the excess risk of vaginal delivery of term breech presentations provided by Sachs *et al.* (1983), Fortney *et al.* (1986), and Bingham & Lilford (1987). It is also of some obstetric interest that, in an analysis of the effects of mode of delivery on mortality among twins born in New York City during the same period (Kiely 1990), heavier twins appeared to be at unusually high risk if they were not born by caesarean section. For twins presenting by the vertex who weighed more than 3000 g, the neonatal death rate was more than four times higher in vaginal births than in caesarean sections.

Nevertheless, the obstetric community needs to carry out a multicentre randomized controlled trial of surgical intervention in breech presentation. Neither in the investigation reported here nor in any of the other non-experimental studies of management of breech presentation

Table 3. Variables controlled in further multivariate regression analysis

Birthweight
Gestational age
Parity
Gravidity
Sex of infant
Mother's age
Marital status
Previous fetal loss
Previous infant deaths
Race
Mother's education
Number of prenatal visits
Time interval from LMP to first prenatal visit
Pregnancy complications*
Complications of labour/delivery†
Type of service (public vs private)
Financial coverage

*Pre-eclampsia, abnormal uterine bleeding, diabetes, other complication, no complication.

†Placental abruption, placenta previa, prolapsed umbilical cord, prelabour rupture of membranes, other complication, no complication.

(Bowes *et al.* 1979; De Crespigny & Pepperell 1979; Sachs *et al.* 1983; Fortney *et al.* 1986; Gimovsky & Paul 1982) can one be sure that selection bias has been controlled. This bias originates partly from obstetricians' decisions to *not* perform a caesarean section in certain extremely high risk mothers and fetuses. Another source of selection bias is the probable over-representation in the vaginal group of emergency deliveries in inappropriate places (for example, emergency rooms). In addition, the results of this New York City study are in conflict with the findings of some previous studies that controlled for birthweight and other confounders. In particular, studies in northern California (Petitti & Golditch 1984), the Netherlands (Schutte *et al.* 1985), and at the Medical Center Hospital of Vermont (Mann & Gallant 1979) reported no excess risk when breech vaginal deliveries were compared to breech caesarean sections.

In the absence of definitive results from a large randomized controlled trial, a scientific policy of management of breech presentation will have to rely on population-based studies like this one and a previous investigation from Georgia, USA (Sachs *et al.* 1983). Both studies found that with breech presentation vaginal delivery had a sub-

stantial excess risk of neonatal mortality compared to caesarean section.

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Maternal serum unconjugated oestriol and human chorionic gonadotrophin levels in twin pregnancies: implications for screening for Down's syndrome

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Abstract

Objective—To investigate maternal serum unconjugated oestriol (uE_3) and human chorionic gonadotrophin (hCG) levels in twin pregnancies and to consider the implications of the results for antenatal screening for Down's syndrome.

Design—Measurement of maternal serum uE_3 and hCG levels from 15–22 weeks of gestation in twin and singleton pregnancies. Previously available maternal serum alpha-fetoprotein (AFP) levels were also presented.

Setting—Stored serum samples collected from women receiving routine antenatal care in Oxford were used.

Subjects—200 women with a twin pregnancy and, for each, three singleton control pregnancies matched for gestational age (same completed week of pregnancy) and duration of storage of the serum sample (same calendar quarter).

Results—The median uE_3 , hCG and AFP levels in the twin pregnancies were respectively, 1.67 (95% CI 1.56–1.79), 1.84 (95% CI 1.64–2.07) and 2.13 (95% CI 1.97–2.31) multiples of the median (MoM) for singleton pregnancies at the same gestational age. The variance of values for the three serum markers (expressed in logarithms), and the correlation coefficients between any two, were similar in the twin and singleton pregnancies.

Conclusion—In maternal serum screening programmes for Down's syndrome dividing uE_3 , hCG and AFP MoM values in twin pregnancies by the corresponding medians for twin pregnancies will, in expectation, yield a similar false-positive rate in twin pregnancies as in singleton pregnancies.

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Antenatal screening for Down's syndrome is achieved by the measurement of maternal serum unconjugated oestriol (uE_3), human chorionic gonadotrophin (hCG) and alpha-fetoprotein (AFP) in the second trimester of pregnancy. It is known that serum AFP levels in twin pregnancies are about double those in singleton pregnancies (see Wald & Cuckle 1984 for a review). It is thought that uE_3 and hCG levels are also high in twin pregnancies but the small numbers of pregnancies so far studied leave uncertainty over the magnitude of the effect (Alpert *et al.*

1990; Bogart *et al.* 1990; Braunstein *et al.* 1978; Canick *et al.* 1990, Crosignani 1974, Jovanovic *et al.* 1977) To determine this and to consider the implications for screening we used stored antenatal serum samples that had been collected as part of an antenatal screening programme for neural tube defects, and measured AFP as well as uE_3 and hCG.

Subjects and methods

The samples used in this study were selected from a large series collected from women having an AFP screening test for neural tube defects in Oxford between 1977 and 1983, and stored at -40°C . We identified the first 200 women who had given birth to twins without Down's syndrome or neural tube defect and who had had a serum sample collected for an AFP test between 15 and 22 weeks gestation. The numbers at each completed week of gestation were, respectively, 19, 62, 58, 29, 8, 13, 9 and 2. For each of these twin pregnancies three singleton pregnancies without Down's syndrome or neural tube defect ('controls') were identified at the same completed week of pregnancy in which a serum sample had been collected and tested in the same calendar quarter. Serum samples from each of these 800 pregnancies were retrieved from storage and assayed for uE_3 and hCG without knowledge of whether the serum related to a twin or a singleton pregnancy. Gestational age was estimated from the first day of the last menstrual period.

The maternal serum uE_3 , hCG and AFP results (the AFP values obtained when the women were originally screened) were expressed in multiples of the median (MoM) for singleton pregnancies at the same gestational age. Singleton medians were derived by using a regression of the median value for the particular substance concerned on gestational age, weighted for the number of pregnancies in each completed week. For AFP and uE_3 , log linear regressions were used; for hCG a constant plus exponential regression was used as described previously (Wald *et al.* 1988).

The correlation coefficients between the log MoM values of each of the markers were estimated after excluding five twin and nine singleton pregnancies with outlying values. An outlier was regarded as any value ≥ 3.5 standard deviations from the log median value where the standard deviation was estimated from the log

90th–10th centile interval divided by 2.563. Such value will occur only rarely just because of random variability.

Results

Table I shows the 10th, median and 90th centile for uE_3 , hCG and AFP among singleton and twin pregnancies. The median uE_3 , hCG and AFP levels in twin pregnancies were 1.67 MoM (95% confidence interval (CI) 1.56–1.79), 1.84 MoM (95% CI 1.64–2.07) and 2.13 MoM (95% CI 1.97–2.31) respectively. The ratio of the 10th centile in twin pregnancies to that in singleton pregnancies was similar to the ratio of the respective median values as was the ratio of the 90th centiles, indicating that on a proportional (or logarithmic) scale the variances of values for the three serum markers were similar in twin and singleton pregnancies. A single estimate of the standard deviation (expressed in logs) could therefore be used to describe the dispersion of each marker in twin and singleton pregnancies.

The correlation coefficients between AFP and hCG, AFP and uE_3 , uE_3 and hCG, were, respectively, 0.05, 0.30 and -0.24 in singleton pregnancies and 0.14, 0.23 and -0.21 , respectively, in twin pregnancies. The coefficients between any pair of serum markers were reasonably similar in twin and singleton pregnancies ($P=0.3$, 0.4 and 0.8 respectively, using Fisher Z transformation).

Discussion

Our study has confirmed that maternal serum AFP values in twin pregnancies are, on average, about twice (2.1) that of singleton pregnancies. On average uE_3 values were 1.7 times as high and hCG values 1.8 times as high. It is well recognised that mid-trimester serum AFP levels in twin pregnancies are double those in singleton pregnancies. There are fewer data on uE_3 and hCG levels in twin pregnancies. Bogart *et al.* (1990) published data on hCG levels in respect of 28 twin pregnancies and did not find any difference compared to singleton pregnancies. Canick *et al.* (1990) reported results (based on 35 twin pregnancies) that were close to our own: the uE_3 and hCG levels were, respectively, 1.7 and 1.9 MoM. Alpert *et al.* (1990), who studied 51 twin pregnancies, obtained uE_3 and hCG values that were somewhat lower, namely 1.4 and 1.8 MoM respectively.

Table 1. 10th, median and 90th centile of maternal serum unconjugated oestriol (uE₃), human chorionic gonadotrophin (hCG) and alpha-fetoprotein (AFP) in 600 singleton and 200 twin pregnancies between 15 and 22 weeks of pregnancy

Serum marker	Centile	Singleton pregnancies (MoM*) [a]	Twin pregnancies (MoM*) [b]	Ratio of values in singletons and twins [b/a]
uE ₃	10th	0.60	1.03	1.7
	Median	1.01	1.67	1.7
	90th	1.50	2.41	1.6
hCG	10th	0.46	0.87	1.9
	Median	0.99	1.84	1.9
	90th	1.97	3.76	1.9
AFP	10th	0.54	1.33	2.5
	Median	0.98	2.13	2.2
	90th	1.69	3.51	2.1

*MoM = Multiple of median for singleton pregnancies estimated by regression

Estimates of the standard deviation for singletons and twin pregnancies were (log₁₀) uE₃ 0.16 and 0.14, hCG 0.24 and 0.25, and AFP 0.19 and 0.16 respectively. (These estimates should not be used directly in specifying the parameters of the distributions for use in screening for Down's syndrome because they do not take account of the usual batch-to-batch assay variance.)

Screening for Down's syndrome involves estimating a woman's risk of an affected pregnancy based on her serum uE₃, hCG, AFP and age. To estimate this risk it is necessary to know the distribution of uE₃, hCG, and AFP values in pregnancies with and without Down's syndrome and the age-specific risk. This is known for singleton pregnancies, and the present study has provided such information for *unaffected* twin pregnancies. The rarity of Down's syndrome in twin pregnancies, however, means that it is extremely difficult to collect comparable data in *affected* twin pregnancies. Nonetheless, the unaffected twin data provide sufficient information to specify a screening policy for twins that would be expected to yield a similar false-positive rate to that in singleton pregnancies. This is achieved by dividing the uE₃, hCG and AFP MoM values by the corresponding median values for twin pregnancies (Table 1), and estimating the risk of Down's syndrome as though it were a singleton pregnancy. This procedure will, in expectation, yield a similar false-positive rate in twin and singleton pregnancies because the standard deviations of the three serum markers and the correlation coefficients between them, are similar in twin and singleton pregnancies.

The Down's syndrome detection rate associated with the policy of adjusting twin values to singleton values cannot be estimated precisely

but it is likely to be less than that for singleton pregnancies because the presence of an unaffected co-twin will tend to bring the distributions for affected and unaffected twin pregnancies relatively closer together compared with affected and unaffected singleton pregnancies.

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Haemorrhagic problems in obstetrics and gynaecology in patients with congenital coagulopathies

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Abstract

Objective—To review the obstetric and gynaecological problems in women with congenital coagulopathies.

Design—Retrospective review.

Setting—Regional Adult Haemophilia Unit, Glasgow Royal Infirmary

Subjects—All women in contact with the Unit over a period of 30 years, comprising eight with von Willebrand's disease, 18 obligate carriers of haemophilia A and five obligate carriers of Christmas disease. Each woman was interviewed and details of their obstetric and gynaecological histories were obtained and their case records were reviewed.

Main outcome measures—Haemostatic changes associated with pregnancy and gynaecological problems.

Results—In 14 pregnancies in seven patients with von Willebrand's disease, there were four primary and four secondary post-partum haemorrhages and a large perineal haematoma complicating an episiotomy. These problems arose despite the endogenous rise in factor VIIIc seen with pregnancy. All women seen with von Willebrand's disease complained of menorrhagia and had been referred to gynaecologists. Treatment included danazol, tranexamic acid and the contraceptive pill. Diagnostic curettage resulted in severe haemorrhage in one woman and two women with pelvic pain and dyspareunia were found to have spontaneous broad ligament haematomas, one requiring surgery. In 43 pregnancies in obligate carriers of haemophilia A and Christmas disease there were five post-partum haemorrhages and a large perineal haematoma.

Conclusion—In von Willebrand's disease it should be noted that adequate laboratory correction of factor VIIIc levels does not ensure clinical haemostasis; hence platelet function should also be measured. Patients with congenital coagulopathies pose particular problems for the obstetrician and gynaecologist and should be managed in close association with the local haemophilia centre

The most common congenital coagulopathies are von Willebrand's disease, haemophilia A and haemophilia B (Christmas disease). von Willebrand's disease constitutes a heterogeneous

group of haemorrhagic disorders, which are usually transmitted as autosomal dominant traits, although autosomal recessive transmission of some variant types occurs (Ingram 1978;

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Italian Working Group 1977) The prevalence of von Willebrand's disease is at least 3–4 per 100 000 in the UK (Bloom 1980), and due to its autosomal pattern of inheritance it is the commonest congenital coagulopathy affecting women. Clinical features are variable and include easy bruising, epistaxis, gastrointestinal and oral bleeding, post-operative and post-traumatic bleeding, menorrhagia and post-partum haemorrhage (Silwer & Nilsson 1964). Severe forms are easy to diagnose, but milder forms occur which may be difficult to diagnose because of intra-individual variations in factor VIII:vWF (including elevations during pregnancy or oral contraceptive use), and which may become apparent only following a major haemostatic challenge. There is a quantitative and/or qualitative reduction in factor VIII:vWF. This macromolecular complex is made up of two specific entities. The first is the procoagulant component of factor VIII, termed factor VIIIc. This is a glycoprotein produced by the liver which plays an important role in the intrinsic pathway of the coagulation cascade. It forms a complex in the circulation with the second entity, von Willebrand factor (vWF), which is produced by the endothelium and megakaryocytes and which is made up of multimers or subunits (Zimmerman & Ruggeri 1982). vWF is measured antigenically as von Willebrand antigen (vWF:Ag) and functionally as ristocetin co-factor which is the ability of platelet-poor plasma to act as a co-factor for ristocetin-induced platelet aggregation. vWF acts as a carrier and stabilizer for factor VIIIc, preventing it from inactivation or catabolism. Deficiency of vWF results in defective platelet-endothelial and platelet-platelet interactions which manifest clinically as bleeding from mucous membranes and a prolonged skin bleeding time. The classic form of von Willebrand's disease (type I) is associated with similar reduction in factor VIIIc, vWF:Ag and ristocetin co-factor, and reduced platelet aggregation to ristocetin. Variant von Willebrand's disease (type II) is characterized by abnormal multimeric structure of vWF (Coller 1984), and discordant reductions in factor VIIIc, vWF:Ag and ristocetin co-factor. A variety of subtypes of type II von Willebrand's disease exist (IIa, IIb, etc), differentiated by multimeric analysis and platelet aggregation to ristocetin.

In contrast to von Willebrand's disease, haemophilia A and Christmas disease are X-linked recessive disorders and among carrier women only about one in ten has excessive bleed-

ing. The prevalence of haemophilia A is 1–2/10 000 in the UK and about one-tenth of this for Christmas disease (Forbes 1984). These conditions are characterized by low levels of factor VIIIc and IX respectively. As women have two X-chromosomes, carriers would be expected to have levels of around 50% of normal for these factors. However, a wide range of functional activities has been reported (Rizza *et al.* 1975) due to Lyonization (Lyon 1962), with some having low levels of factor VIIIc (10–40 iu/dl) and haemorrhagic problems (Lusher & McMillan 1978). In contrast to von Willebrand's disease, haemophiliacs have normal bleeding times as platelet function is unaffected, and do not usually suffer from cutaneous bleeding; however, they suffer deep tissue bleeds, haemarthroses and post-operative bleeding (Forbes 1984). It has been established that the factor VIII:vWF complex increases in normal pregnancy and also in carriers of haemophilia and women with von Willebrand's disease (Noller *et al.* 1973; Bennett *et al.* 1974; Telfer & Chediak 1977; Takahashi 1983; Hill *et al.* 1982; Hanna *et al.* 1981; Krishnamurthy & Miotti 1977), although the increase in ristocetin co-factor has not been a consistent finding in patients with von Willebrand's disease (Adashi 1980). These increases may be important in protecting women from the haemorrhagic challenge of delivery.

There is little literature on the obstetric and gynaecological problems in women with von Willebrand's disease and carriers of haemophilia A and Christmas disease. The aim of this study was to review the obstetric and gynaecological problems of such women attending the West of Scotland Regional Haemophilia Unit.

Patients and methods

Eight women with von Willebrand's disease, 18 obligate carriers of haemophilia A and 5 obligate carriers of Christmas disease who were registered with the Regional Adult Haemophilia Unit, Glasgow Royal Infirmary were studied. These represented all female patients in contact with the unit and the pregnancies occurred over a 30-year period. Each patient was interviewed and details of their obstetric and gynaecological histories were obtained. Case records relating to these and their coagulation status were reviewed. Disease severity was assessed clinically. Laboratory assessment of patients with von Willebrand's disease included skin bleeding time (Ivy

method), factor VIIIc (one-stage assay), vWF:Ag (Laurell rocket immunoelectrophoresis assay) and ristocetin co-factor (assessed using formalin fixed platelets). Obligate carriers of haemophilia A had factor VIIIc and vWF:Ag measured and obligate carriers of Christmas disease had factor IXc measured. Fifty-nine pregnancies in these women were reviewed; 14 in the von Willebrand's group, 11 in the carriers of Christmas disease and 34 in the carriers of haemophilia A. These exclude first trimester losses and ectopic pregnancies, which are included in the gynaecological assessment. Laboratory assessments of coagulation factors during the third trimester were available for five women with von Willebrand's disease, four of the five Christmas disease carriers, and 13 carriers of haemophilia A.

Results

The haemostatic, obstetric and gynaecological details of the von Willebrand's disease patients are shown in Tables 1, 2 and 3 respectively, together with the haemostatic changes associated with pregnancy (Fig. 1). The 14 pregnancies were complicated by four primary and four secondary post-partum haemorrhages. Five of these occurred despite cryoprecipitate treatment following delivery, and five women required blood transfusion. A large perineal haematoma also developed in an episiotomy wound. These problems arose despite a substantial increase in factor VIIIc during pregnancy in 3 of the 5 women where measurements were made. All eight women with von Willebrand's disease had been referred to a

gynaecologist at some time because of menorrhagia, most because of prolonged menses and three had had a diagnostic curettage. In patients 1 and 3 (Table 1) no blood products were given prophylactically and no haemostatic problems were encountered at curettage. One (no. 6) had had a diagnostic curettage, at 14 years of age because of menorrhagia, without haemostatic cover. She had a major primary post-operative haemorrhage which required blood transfusion, cryoprecipitate and uterine packing. Seven of the eight women had been treated with the combined oral contraceptive pill for menorrhagia with good benefit in three, only slight improvements in three and without effect in one. Tranexamic acid was used in two women for menorrhagia without benefit. One woman was treated successfully with danazol when neither the oral contraceptive pill nor tranexamic acid had been successful.

Two women (nos 3 and 4; Table 3) had been sterilized by a 'mini-laparotomy' technique and were given cryoprecipitate. One of them (no. 4) had no haemostatic problem but the other (no. 3) developed a wound haematoma. Two patients (nos. 3 and 7) had been treated for broad ligament haematomas. One of them (no. 7) developed a spontaneous broad ligament haematoma after stopping the oral contraceptive pill. This was initially suspected to be an ectopic pregnancy but a broad ligament haematoma was diagnosed by ultrasound and laparoscopy. This was treated conservatively with cryoprecipitate infusions with satisfactory resolution. In patient no. 3 symptoms of dyspareunia, left iliac fossa pain and tenderness and cystic swelling of the left adnexa on ultrasound, led to suspicion of either a broad

Table 1. Haemostatic data for eight women with von Willebrand's disease

Patient no	von Willebrand's type/sub type	Clinical severity	Factor VIIIc (iu/dl) *	vWF Ag (iu/dl) *	RCF (iu/dl) *	Bleeding time (min)
1	IIA	Moderate	74 (N/A)	67 (N/A)	17 (N/A)	>20 (N/A)
2	IIA	Moderate	52 (N/A)	34 (N/A)	11 (N/A)	>20 (N/A)
3	IIG	Mild	12 (45)	22 (25)	30 (N/A)	>20 (N/A)
4	I	Mild	26 (58, 55)	25 (23, 25)	11 (20, N/A)	>20 (9.5)
5	IIG	Mild	28 (62, 58)	19 (80, 84)	<10 (<10)	>20 (>20)
6	I	Mild	44 (100)	20 (62)	22 (20)	>20 (N/A)
7	IIA	Moderate	34 (120, 110)	34 (115, 101)	11 (<10, <10)	>20 (>20)
8	I	Mild	31	67	<10	>20

*Non-pregnant levels of factor VIII components are shown with third trimester levels in parenthesis, where data are available for more than one pregnancy these are shown in parenthesis in chronological order of pregnancies. Reference range >45 iu/dl

N/A, Data not available RCF, Ristocetin cofactor

Table 2. Obstetric details of eight women with von Willebrand's disease

Patient no.	Pregnancy no.	Delivery	Haemorrhagic problems	Cryoprecipitate cover	Blood transfusion
1	1	SVD	1 ^Y PPH	No*	Yes
	2	SVD	1 ^Y PPH	No*	No
	3	SVD	None	No*	No
2	1	FD	1 ^Y PPH/2 ^Y PPH	Yes	Yes
3	1	SVD	2 ^Y PPH	Yes	No
	2	SVD	2 ^Y PPH†	Yes	Yes
4	1	SVD	None	No	No
	2	CS	None	Yes	No
5	1	SVD	1 ^Y PPH, threatened miscarriage	Yes	Yes
	2	SVD	None	Yes	No
6	1	SVD	None	No	No
7	1	SVD	2 ^Y PPH	Yes	Yes
	2	SVD	None	Yes	No
	3	SVD	None	Yes	No
8	0	—	—	—	—

*Disease not diagnosed at time of delivery.

†Major secondary PPH despite cryoprecipitate infusion producing a plasma factor VIIIc level of >150 IU/dl. Epsilonaminocaproic acid treatment, ergometrine and oxytocin i.v. infusion and uterine packing were required to control bleeding.

1^YPPH, Primary post-partum haemorrhage; 2^YPPH, Secondary post-partum haemorrhage; SVD, Spontaneous vaginal delivery; FD, Forceps delivery, CS, Caesarean section

ligament haematoma or a haemorrhagic ovarian cyst. Conservative management with cryoprecipitate did not resolve the symptoms and at laparo-

tomy, with additional cryoprecipitate cover, there was a haemorrhagic corpus luteum cyst and a large broad ligament haematoma. The haema-

Table 3. Gynaecological details of eight women with von Willebrand's disease

Patient no	Referral for menorrhagia	Usual menstrual cycle	Towels/tampons used per day	Treatment of menorrhagia and its effect	Other gynaecological problems
1	Yes	7/28	5	D&C×2—No effect	—
2	Yes	7–10/14–28	2	OCP—Slight improvement	—
3	Yes	6/28	6	Tranexamic acid—No effect OCP—Good effect	(i) Sterilization (ii) Broad ligament haematoma
4	Yes	10/28	8	D&C×2—No effect Tranexamic acid—No effect OCP—Slight improvement Danazol—Good effect	Sterilization
5	Yes	10/28–35	6	OCP—Good effect	—
6	Yes	7–10/28	8	D&C—No effect (provoked major haemorrhage) OCP—Slight improvement	—
7	Yes	10/28	8	OCP—Good effect	Broad ligament haematoma
8	Yes	5/28	10	OCP—No effect	—

D&C, Diagnostic curettage. OCP, Combined oral contraceptive pill.

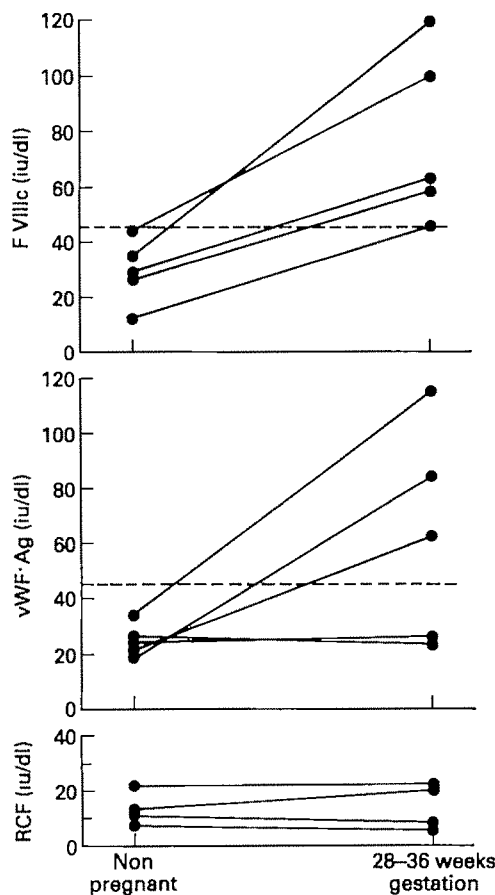


Fig. 1. Changes in coagulation factors in pregnancy in women with von Willebrand's disease. Where women have had more than one pregnancy only changes occurring in their first pregnancy have been illustrated (normal values are >45 iu/dl indicated by broken line on the figure)

toma was drained and a left salpingo-oophorectomy performed. Cryoprecipitate was given daily for 10 days post-operatively: despite this a wound haematoma developed.

Thirty-four pregnancies in 18 obligate carriers of haemophilia A were reviewed. Most of them had a substantial increase in factor VIIIc by 28–36 weeks gestation, with all but two attaining normal concentrations (>45 iu/dl). vWF:Ag also increased (Fig. 2). There were 23 spontaneous vaginal deliveries, seven forceps deliveries, and four caesarean sections. No antepartum haemorrhages occurred, but three carriers had secondary post-partum haemorrhages, two of which were associated with retained products of conception following vaginal delivery and required evacuation of the uterus and blood transfusion. Both

these carriers had normal concentrations of factor VIIIc in the third trimester (97 iu/dl and 76 iu/dl). The third secondary post-partum haemorrhage occurred after an elective caesarean section. The patient had a low concentration of factor VIIIc in the non-pregnant state (13 iu/dl) and during pregnancy (19 iu/dl). She was treated with cryoprecipitate for 7 days after delivery and allowed home 10 days after delivery without complications. However, 4 weeks after delivery she presented with a secondary post-partum haemorrhage of over 1000 ml. This was thought to be related to endometritis and she was successfully treated with cryoprecipitate, antibiotics and tranexamic acid.

Four of the 18 obligate carriers of haemophilia A had sought gynaecological advice for menorrhagia, and all had had diagnostic curettage performed without complication. Three had factor VIIIc and vWF:Ag concentrations within the normal range. The fourth had a slightly low factor

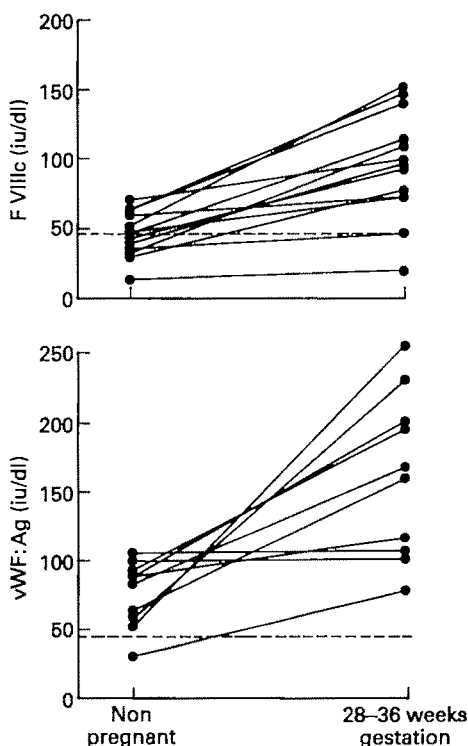


Fig. 2. Changes in factor VIIIc and vWF:Ag in obligate carriers of haemophilia A during pregnancy. Where carriers have had more than one pregnancy, only the changes occurring in their first pregnancy are illustrated (normal values are >45 iu/dl indicated by broken line on the figure)

Table 4. Obstetric details for five obligate carriers of Christmas disease

Patient no.	Factor IXc (iu/dl)	Pregnancy no.	Outcome/delivery	Haemorrhagic problems	Blood products given	Blood transfusions
1	10 (21)	1	SVD	Perineal haematoma	FFP	Yes
		2	SVD	None	FFP	No
2	30 (43, N/A, 46†, 45†)	1	SVD	None	No	No
		2	Missed miscarriage (evacuation)	None	FFP	No
		3	Prostaglandin termination‡	None	FFP	No
		4	Prostaglandin termination‡	None	FFP	No
3	17 (N/A)	1	C/S	None		No
		2	C/S	None		No
4	4 (4)	1	FD	None	FFP	No
		2	SVD	None	FFP	No
5	10 (29, 22)	1	FD	None	FFP	No
		2	SVD	2 ^y FPH	FFP	No

FFP, Fresh frozen plasma, 2^yPPH. Secondary post-partum haemorrhage; SVD, Spontaneous vaginal delivery, FD, Forceps delivery, CS, Caesarean section

*Factor IX levels are shown with third trimester value in parentheses, where data are available for more than one pregnancy these are shown in the parentheses in chronological order of pregnancies. Normal values are >45 iu/dl

†Factor IX level taken during second trimester.

‡Prostaglandin termination at 18 weeks for genetic disease

VIIIc concentration (40 iu/dl) and she was given cryoprecipitate pre-operatively. All diagnostic curettages were uncomplicated. Three of these women went on to have abdominal hysterectomies. One, with baseline factor VIIIc concentration of 40 iu/dl developed a vault haematoma and was treated with factor VIII concentrate infusions for one week. The other two patients had no haemostatic problems associated with their operations. One received prophylactic cryoprecipitate as the factor VIIIc concentration was 47 iu/dl and she had a history of haemorrhage following cone biopsy. The other, with factor VIIIc levels of 60 iu/dl received no blood product cover for hysterectomy. Other gynaecological problems included an ectopic pregnancy associated with major haemorrhage in the patient with a factor VIIIc concentration of 40 iu/dl, four miscarriages and uterine evacuations not associated with any haemorrhagic complication, and a sterilization and hysterotomy for termination of pregnancy which was uncomplicated.

The obstetric details and factor IXc concentrations in the five obligate carriers of Christmas disease are shown in Table 4. These women showed less increase in factor IX during preg-

nancy, compared with the increase in factor VIII seen in the haemophilia A carriers. All but one of their deliveries were covered with fresh frozen plasma given immediately post partum. There was one secondary post-partum haemorrhage and one perineal haematoma which occurred before plasma treatment.

Two of the obligate carriers of Christmas disease had menorrhagia. Patients 1 and 3 (Table 4) had had a diagnostic curettage with prophylactic administration of fresh frozen plasma, patient no. 3 subsequently underwent oophorectomy for pelvic pain, then abdominal hysterectomy for menorrhagia. She received fresh frozen plasma prophylaxis for both procedures. None of these gynaecological operations was complicated by haemorrhage.

Discussion

This review of gynaecological problems in patients with von Willebrand's disease highlights the common occurrence of menorrhagia in these patients and is in keeping with the findings of Wendt & La Fond (1960), Hill & Taylor (1968); Nilsson & Blomback (1963) and Evans (1971).

Menorrhagia is difficult to quantify, but all the women reviewed here had been referred to gynaecologists because of this. Although von Willebrand's disease is not a common disorder, it should be considered in the assessment of women with menorrhagia, and a family history and enquiry about other bleeding problems is of value in such patients. The diagnosis of a coagulopathy such as von Willebrand's disease will have a major influence both on the assessment and treatment of menorrhagia. Operative procedures should not be undertaken lightly in these patients as even relatively minor procedures such as diagnostic curettage may result in substantial post-operative haemorrhage if no haemostatic cover is used, as occurred in patient no. 6 (Table 3), and in the reports by Hill & Taylor (1968) and Evans (1971). Such operative assessment or treatment should be managed with the local haemophilia unit and adequate haemostatic cover provided. The combined oestrogen-progesterone contraceptive pill appears to be of most value in the treatment of menorrhagia in women with von Willebrand's disease. This response may be related to increased levels of factor VIIIc and vWF seen with oestrogen therapy (Coller 1984). The alternative treatment with the anti-fibrinolytic agent tranexamic acid was considered to be ineffective by the two women treated with it. A further possible treatment is danazol which was successful in one woman (Table 3, no. 4) in whom tranexamic acid and the combined oral contraceptive pill were relatively ineffective. However, danazol may theoretically promote bleeding by promoting fibrinolysis. Hysterectomy may sometimes be indicated in these patients (Evans 1971).

This series includes two patients with broad ligament haematomas, one arising spontaneously and the other secondary to a haemorrhagic corpus luteum. This has not been reported previously in von Willebrand's disease, but is an important diagnosis to consider before embarking on any surgical procedure with its possible complications. Haematomas are best managed conservatively with infusions of factor VIII:vWF concentrates to prevent further bleeding and to allow spontaneous resorption of the haematoma. If conservative treatment is unsuccessful, then operative intervention may be required with appropriate haemostatic cover.

Cryoprecipitate has been the treatment of choice for severe bleeding episodes and surgical procedures in von Willebrand's disease (Coller 1984). It was thought to be preferable to high

potency factor VIII concentrates, which contain fewer high molecular weight multimers and do not elevate ristocetin cofactor or shorten skin bleeding time as effectively as cryoprecipitate (Coller 1984). However, there is also considerable variability in the correction of bleeding times following treatment with cryoprecipitate, and even the laboratory assessment of vWF activity (ristocetin co-factor) does not permit reliable prediction of clinical response (Coller 1984). Following the recent epidemics of human immunodeficiency virus (HIV) (Darby *et al.* 1989) and hepatitis in haemophiliacs (and some patients with von Willebrand's disease) following treatment with non-heat-treated blood products, their use has decreased. None of the cryoprecipitate treatments described in the present series was followed by seroconversion for HIV, hepatitis B, or hepatitis C virus or by clinical or laboratory evidence of hepatitis. Nevertheless it is important in all patients with congenital coagulopathies, who may require treatment with blood products, to maintain immunity against hepatitis B by vaccination and to consider the risks of virus transmission (relative to risks of bleeding) before treatment with blood products. The current choice of product is determined not only by its content of haemostatically effective high molecular weight multimers of vWF, but also by its safety record (i.e., transmission of non-A non-B hepatitis and transfusion reactions). NHS 8Y (Elstree) factor VIII concentrate or Haemate P (Behringwerke) is recommended. Where the haemostatic efficiency is in doubt, cryoprecipitate should be considered, but it has a higher risk of non-A non-B hepatitis and transfusion reactions.

In recent years, an alternative to blood products for normalizing factor VIII:vWF levels in von Willebrand's disease, mild haemophilia A and haemophilia carriers with low factor VIIIc levels has been the slow intravenous infusion of the synthetic analogue of antidiuretic hormone (vasopressin) known as desmopressin (Mannucci *et al.* 1987; Mannucci 1988). This treatment releases endogenous factor VIII:vWF from vascular endothelium, and has been used successfully for both treatment and prophylaxis of bleeding, including haemostatic cover of gynaecological surgery. Side effects of desmopressin include facial flushing, nausea, fluid retention which may cause symptomatic hyponatraemia especially after surgery (Lowe *et al.* 1977), and myocardial infarction (O'Brien *et al.* 1989; van

Dantzig *et al.* 1989; Lowe 1989). Nevertheless, desmopressin should always be considered before use of blood products. Because desmopressin also stimulates release of tissue plasminogen activator from vascular endothelium, thus increasing fibrinolytic activity, some have advocated concomitant treatment with antifibrinolytic agents such as tranexamic acid; however, this is not usually considered necessary. Because of reports of thrombosis, caution is advised for the use of desmopressin in pregnant women and in patients with arterial disease and concomitant use of antifibrinolytic agents in such patients should be avoided. In such cases the balance of risks may favour blood product therapy.

von Willebrand's disease is also important in obstetric practice. von Willebrand *et al.* (1934) noted that these patients were at less risk of haemorrhage during the antenatal period, but were at high risk of post-partum haemorrhage. This is likely to be associated with the increase in factor VIII seen during pregnancy, and the rapid fall following delivery (Krishnamurthy & Miotti 1977; Noller *et al.* 1973). Our results of a high rate of post partum haemorrhage are in keeping with previous reports (Wendt & La Fond 1960; Hill & Taylor 1968; Noller *et al.* 1973; Evans 1971). In the present study the two patients with type I von Willebrand's disease showed an increase in factor VIIIc to concentrations >50 iu/dl by the third trimester. Neither had any haemorrhagic problems, and cryoprecipitate was used in only one, as delivery was by caesarean section. All the patients with variant von Willebrand's disease, however, had post-partum haemorrhages despite some having similar increases in factor VIIIc and this occurred despite treatment with cryoprecipitate. Women with von Willebrand's disease increase their factor VIIIc and vWF:Ag concentrations during pregnancy as do normal women and this is confirmed in this study, although changes in ristocetin cofactor and bleeding time are more variable. There are only three previous reports of variant von Willebrand's disease (2 type IIA; 1 type IIB) in pregnancy. In both cases with type IIA these women increased their factor VIIIc, vWF and ristocetin cofactor to normal concentrations (Hanna *et al.* 1981; Takahashi 1983) and neither suffered any significant post-partum haemorrhagic problem. However, in the case reported by Takahashi (1983) qualitative analysis of vWF:Ag showed that the large multimers of vWF:Ag did not appear in blood during gestation. These large multimers have high resto-

cetin cofactor activity and are important for platelet adhesion and primary haemostasis (Zimmerman & Ruggeri 1982), and this may explain why these patients appear to be at greater risk of haemorrhage than those with type I von Willebrand's disease. Patients with type IIB von Willebrand's disease may pose slightly different problems. They can develop thrombocytopenia due to binding of the abnormal intermediate sized multimers of vWF:Ag to platelets and inducing spontaneous platelet aggregation and subsequent thrombocytopenia (Rick *et al.* 1987). This is more likely to occur in pregnancy, when there is a stimulus to vWF:Ag production resulting in a high concentration of these abnormal multimers. Such patients need careful monitoring in pregnancy and may require treatment with both platelets and vWF containing blood products (Rick *et al.* 1987).

It has been suggested that no blood products are required to cover delivery in women with von Willebrand's disease if factor VIIIc concentrations rise to over 50 iu/dl (Telfer & Chediak 1977). However, it seems that there is a poor correlation between bleeding complications in pregnancy and the degree to which the coagulation factors have improved (Takahashi 1983). Furthermore there appears to be no correlation between increases in factor VIIIc, vWF:Ag, ristocetin cofactor or bleeding time (Hill *et al.* 1982; van Royen *et al.* 1974). It is difficult therefore to predict from a haemostatic assessment during pregnancy which women are most at risk from haemorrhage. There is also great variability in the response to pregnancy between individuals, although our results suggest that this is consistent within individuals over several pregnancies.

In the management of women with von Willebrand's disease in pregnancy it is important to establish the type and to monitor haemostatic variables especially in the third trimester. In patients with type I von Willebrand's disease an increase in factor VIIIc or levels to >50 iu/dl appears to be sufficient to allow an uncomplicated vaginal delivery to be carried out safely without blood product cover. However, patients with variant von Willebrand's disease are less likely to achieve an uncomplicated delivery even with similar increases in factor VIIIc. We would advocate therefore that vWF containing blood products be given immediately post-partum to all women with variant von Willebrand's disease and those with type I von Willebrand's disease who have shown an inadequate response in terms of

factor VIIIc. In addition we would suggest that all those delivered by caesarean section be treated with blood products.

One particular situation where haemorrhage may occur is after first or second trimester miscarriage. The concentrations of factor VIIIc seem to peak at around 38 weeks gestation (Noller *et al.* 1973).

The protective effect of pregnancy on factor VIII may not be sufficient at the time of miscarriage to offer haemostatic protection (Sorosky *et al.* 1980; Punnonen *et al.* 1981), and these women should receive adequate cover.

There is very little published information on the obstetric and gynaecological problems of obligate carriers of haemophilia A and Christmas disease, because most of them have factors VIIIc or IXc levels within the normal range, although a wide range of values has been reported. In a study of carriers of haemophilia A, the mean value for factor VIIIc was 54 iu/dl (range 22–116 iu/dl) compared to a normal mean value of 96 iu/dl (range 44–136 iu/dl) (Rizza *et al.* 1975) while 2% of haemophilia A carriers will have levels of factor VIIIc of >30 iu/dl (Rapaport *et al.* 1961). The present study shows similar results with a non-pregnant mean value of 45 iu/dl (range 13–70 iu/dl) for factor VIIIc. Thus most of these women are unlikely to experience major bleeding problems, although a recent study has shown them to be significantly more at risk of bruising, prolonged bleeding from small wounds, haemorrhage after surgical procedures and also following delivery (Bunschoten *et al.* 1988). These authors have shown an association with the level of factor VIIIc or factor IXc by logistic regression analysis. Other reports have noted post-partum haemorrhage in such women (Briet *et al.* 1982; Wahlberg 1982). Menorrhagia has also been reported in these patients (Lusher *et al.* 1978) although in the study of Bunschoten *et al.* (1988) the incidence was not significantly different from a reference group. In the present study we did not find an excessive frequency of menorrhagia, although one haemophilia A carrier developed a vault haematoma after hysterectomy. In the carriers of haemophilia A there was a substantial increase in factor VIIIc and vWF:Ag during pregnancy with almost all patients developing levels within the normal range. Although these patients are less likely to have haemorrhagic problems at delivery, it is important to monitor levels as they can remain low especially in women with low non-pregnant

values. This is illustrated by our patient in whom the concentration of FVIIIc increased from 13 iu/dl to only 19 iu/dl by the time of delivery. Such patients will require blood product cover and are at risk of post partum haemorrhage.

In contrast to carriers of haemophilia A, carriers of Christmas disease seem to have much less of an increase in factor IXc levels with pregnancy. None of the Christmas disease carriers reported here had levels within the normal range before delivery. This was noted by Briet *et al.* (1982) who reported one carrier whose factor IXc level remained low and who had prolonged bleeding post-partum. Again it is important to monitor factor IXc levels during pregnancy, and post-partum factor IX concentrate should be employed if factor IXc levels are inadequate.

In conclusion, patients with von Willebrand's disease, and obligate carriers of the haemophilias may pose particular problems for the obstetrician and gynaecologist and should be managed in close association with the local haemophilia centre.

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Magnesium intake and status and pregnancy outcome in a Danish population

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Abstract

Objective—To investigate the relation between pregnancy outcome and magnesium intake and status.

Design—A prospective observational study in which the estimate of nutrient intake and serum samples were obtained before the final outcome of pregnancy was known. A second part of the investigation was a cross-sectional comparison of magnesium status of normal pregnant women and women with certain pathological pregnancies.

Setting—Antenatal clinic associated to the University Clinic of Obstetrics and Gynaecology, University of Aarhus, Denmark.

Subjects—1203 consecutive women in the 30th week gestation were invited to participate in the study, 991 (82.4%) accepted and records for 965 (80.2%) were available for analysis.

Data—Food intake data were collected by a combination of a self administered questionnaire and a structured interview of a dietary history type. Serum samples were obtained from blood withdrawn in the 30th and 37th week gestation. Obstetric data were collected from the midwifery and hospital records. For a second part of the investigation, biopsies from the uterus and the abdominal rectus muscle were obtained from women delivered by caesarean section.

Results—In the women with normal pregnancies and in the three groups of pathological pregnancies (pre-eclampsia, SGA-infants and preterm labour) the average magnesium intake was within the range of 200 to 208 mg per 1000 kcal per day (SD 32) and there were no differences between the groups. Neither were differences in serum magnesium observed. Birthweight for gestational age was not influenced by magnesium intake. No differences in magnesium status as assessed by determination of magnesium content in muscle biopsies were found between the normal pregnancies and women with pre-eclampsia, SGA-infants or preterm labour.

Conclusion—The intake of magnesium seemed adequate, and pre-eclampsia, SGA-infants, or preterm labour did not seem associated with a low dietary intake of magnesium or magnesium deficiency. Routine magnesium supplementation during pregnancy is not recommended for populations of relative good socio-economic status.

In recent years much attention has been paid to the possible influence of magnesium on normal development of pregnancy. It has been proposed

that the intake of magnesium among pregnant women may be deficient leading to a negative magnesium balance (Ashe *et al.*, 1979; Franz

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1987, Wynn & Wynn 1988). The observation that withdrawal of magnesium from the extracellular medium caused vasoconstriction in human isolated umbilical vessels has led to the hypothesis that magnesium deficiency during pregnancy may involve a risk of developing pregnancy-induced hypertension or intrauterine growth retardation through uteroplacental vasoconstriction (Altura *et al.* 1983; Isery & French 1984). In line with this view, two prospective, randomized trials concluded that magnesium supplementation during pregnancy could be beneficial with regard to birthweight, frequency of preterm labour and pre-eclampsia (Kovacs *et al.* 1988; Spätling & Spätling 1988). In contrast, however, another prospective, randomized study did not show any benefit from such supplements (Sibai *et al.* 1989). However, only Sibai *et al.* (1989) provided data on dietary magnesium intake, and the conflicting results might be explained by different basal levels of magnesium intake. The renal excretion of magnesium in women with pre-eclampsia, with or without fetal growth retardation, was found to be of same order as that in normal pregnant women in a cross-sectional study (Roelofson *et al.* 1988) suggesting that pre-eclampsia may not be associated with magnesium deficiency.

In several countries, including Denmark, the recommendation for magnesium supplementation during pregnancy is growing and is particularly pronounced in the lay press. But as stated by Hibbard (1989) the background for these recommendations is not very convincing. Thus, it remains to be elucidated whether the dietary intake of magnesium during pregnancy is inadequate in general, and whether pre-eclampsia or intrauterine growth retardation are associated with magnesium deficiency.

In this study magnesium intake was assessed in a Danish population of pregnant women characterized by generally good socio-economic status. Data were collected in the 30th week of pregnancy before the disorders in question had developed. The relation between the magnesium intake and serum-magnesium and the development of pregnancy-induced hypertension, small-for-gestation (SGA) infants and preterm labour was considered. In addition the magnesium status, assessed by measurements of the magnesium content in skeletal muscle, was compared between normal pregnancies and pregnancies complicated by pre-eclampsia SGA-infants, or preterm labour.

Subjects and methods

The study was approved by the ethics committee of the County of Aarhus.

Women were recruited between April 15th 1988 and January 15th 1989 when attending one of two antenatal clinics in Aarhus, which was associated to the University Clinic of Obstetrics and Gynecology, University of Aarhus. Only those living in Aarhus town and in certain designated areas around the town, who were not likely to be moving from the area before labour and who were in the 30th week gestation, were eligible for the study. The women had been informed in a letter about the investigation and were asked to participate. Women belonging to foreign cultures were not included in the study because of difficulties with the language. Of the 1203 women eligible, 991 (82.4%) accepted the invitation and entered the study. From 26 women (2.2%) diet records or blood samples were lost for unexplained reasons. Overall 965 (80.2%) women could be assessed by diet records and pregnancy outcome. Subsequently, clinical data were obtained concerning pregnancy, delivery and neonatal period for those women who were eligible but who did not participate in the study.

Another part of the investigation involved women delivered by caesarean section because of pre-eclampsia ($n = 12$), intrauterine growth retardation ($n = 5$), or normal pregnancy but with difficulties in labour ($n = 14$). Their permission was obtained for a biopsy from the uterus and the abdominal musculature during the operation.

Energy and nutrient intake

At entry into the study (30th week gestation) information about food intake during the preceding 3 months was collected by a trained technician using a structured interview of a dietary history type in addition to a self administered questionnaire. Traditionally, Danish food habits consist of a rather small, usually cereal based breakfast, a cold lunch with sandwiches and a cooked evening meal. The questionnaire related to foods that could be readily quantified by the participants such as breakfast items, fruit and drinks. The subjects were asked to record the number of intakes per day or week of these selected food items or food groups and, when relevant to estimate the relative frequency of food items such as sandwich fillings. Special

Immunocytochemical localization of neutrophil elastase in term placenta decidua and myometrium in pregnancy-induced hypertension

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Abstract

Objective—The aim of the study was to determine whether there was evidence of elastase containing neutrophils at the materno-fetal interface in women with pregnancy-induced hypertension (PIH).

Design—An observational prospective study.

Setting—The Simpson Memorial Maternal Pavilion Edinburgh.

Methods—Placentas were obtained at vaginal or abdominal delivery from 51 consecutive women, 23 had normal pregnancies (13 caesarean sections) and 28 had PIH (18 caesarean sections). An immunocytochemical technique was used to localize elastase containing neutrophils in the placenta, decidua and myometrium.

Main outcome measures—The numbers of positively stained cells, estimated subjectively as minimal, moderate or heavy, in subchorionic plate, perivillous fibrin and decidua.

Results—In both normal and PIH pregnancies neutrophils were absent from the myometrium. However, elastase containing neutrophils were located in areas of fibrin in the subchorionic plate and around the villi although there was no significant difference between the normal and PIH group. Neutrophils were also located in the fibrin of the decidua and in this case the number was significantly greater in the PIH group than in the normal group and correlated with plasma urate.

Conclusion—The release of neutrophil elastase in the decidua could contribute to the vascular damage evident in PIH.

Neutrophil activation has been implicated in a number of vascular disorders (Harlan 1987). The azurophilic granules of neutrophils contain a number of substances which are released when cell activation occurs and can cause extensive

vascular damage. These mediators include neutrophil elastase, a protease which can destroy endothelial cells and their basement membranes, together with the subendothelial matrix (Harlan 1987). The release of proteases such as

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elastase is accompanied by free radicals and leukotrienes that can also produce vascular damage and dysfunction.

Pregnancy-induced hypertension (PIH) is a condition characterized by vascular damage to the maternal vessels of the placental bed (Dixon & Robertson 1958). In a recent study, Greer *et al.* (1989) measured plasma neutrophil elastase in the peripheral circulation of women with PIH and compared the values with those of women with normal pregnancies. Their results showed that, in PIH, the levels of plasma neutrophil elastase were increased, indicating that neutrophil activation occurs in this condition. It is possible that in PIH neutrophil activation takes place at the materno-fetal interface and may contribute to the pathogenesis of the necrotizing arteriopathy seen in the vessels of the placental bed. The aim of this study was to determine whether there was evidence of elastase containing neutrophils at the materno-fetal interface of pregnancies complicated by PIH. We have therefore studied the placenta, decidua and myometrium as possible sites of neutrophil activation in PIH. An immunocytochemical technique at the light microscope level was employed.

Subjects and methods

All specimens were obtained from patients at the Simpson Memorial Maternity Pavilion, Edinburgh. Placentas were obtained either following vaginal delivery or following caesarean section from consecutive women agreeing to take part in the study in each group. In the normal group caesarean section was performed for breech presentation or cephalopelvic disproportion in otherwise uncomplicated pregnancies. Twenty-three placentas were obtained from normal pregnancies, and 28 from pregnancies with PIH. Placental bed tissues were obtained from 13 normal and 18 pregnancies with PIH at caesarean section by cutting a wedge of tissue from the central area of the placental bed and inserting a haemostatic suture when required. Pregnancy-induced hypertension was defined as a persistent elevation of diastolic blood pressure >90 mmHg in the second half of pregnancy in women who had been normotensive before 20 weeks gestation. Most of the patients with PIH had proteinuria. The patient details are given in Table 1.

A full thickness block from the fetal to the maternal side was taken from the central region

of each placenta. All samples were washed thoroughly in phosphate buffered saline (PBS) pH 7.4, fixed in 10% formalin saline and embedded in paraffin. A number of 5 µm sections were prepared. One section from each block of placenta was stained with haematoxylin and eosin whilst an adjacent section was stained for neutrophil elastase by an immunocytochemical technique. Sections from placental bed biopsies were prepared and stained in a similar fashion but in addition they were stained with an antibody to cytokeratin.

Neutrophil elastase was localized by the peroxidase-anti-peroxidase technique (Sternberger & Joseph, 1979). Sections were dewaxed and endogenous peroxidase activity was removed by immersing the sections in a freshly prepared solution of 0.5% hydrogen peroxide in methanol for 30 min. Subsequently, the sections were washed in PBS (5 min) and then exposed to normal rabbit serum (1/10 in PBS) for 10 min. The sections were drained and sheep antiserum to neutrophil elastase (ICN Biochemicals Ltd) was applied (1/1000 PBS with 5% bovine serum albumin). The slides were left overnight at 4°C and then washed in PBS.

Subsequently a solution of 10 µl rabbit anti-serum to goat immunoglobulins (DAKO), 50 µl normal human serum and 950 µl PBS was applied to the sections for 30 min. Goat and sheep species are immunologically identical (Esteves & Binaghi 1972), so secondary antibodies can be used interchangeably. Normal

Table 1. Characteristics of women with and without pregnancy-induced hypertension (PIH)

Variable	PIH (n = 28)	Normal (n = 23)
Age (years)	28.0 (5.4)	25.2 (4.7)
No. of primigravid	22	12
Gestational age at delivery (weeks)	34.7 (4.1)*	38.8 (3.1)
Birthweight centile	46.0 (27.3)**	64.2 (30.5)
Mode of delivery:		
Caesarean section	18	13
Vaginal	10	10
Platelet count ($\times 10^9/l$)	109 (46.1)	—
Plasma urate ($\mu\text{mol/l}$)	0.41 (0.8)	—
Number with proteinuria (>0.3 g/24 h)	23	—

* $P < 0.0005$.

** $P < 0.05$.

Data are shown as mean (SD) values.

human serum was added to abolish cross-reactivity (DAKO product list). After washing in PBS, goat peroxidase-anti-peroxidase (DAKO) was applied at a dilution of 1/100 in PBS for 30 min. Sections were washed in PBS and treated with 0.05% 3,3'-diaminobenzidine tetrahydrochloride (DAB) (Sigma) with 0.01% H_2O_2 in PBS for 5 min. Sections were washed in PBS, counterstained in Carazzi's haematoxylin and mounted in DPX. For control sections sheep antiserum to neutrophil elastase was replaced with normal sheep serum (Serotec).

It is difficult to identify trophoblast in the placental bed in haematoxylin and eosin stained sections. Positive identification of trophoblast was required to ensure that the tissue obtained at biopsy did originate from the placental site. Trophoblast was identified by the use of an antibody of cytokeratin, CAM 5.2 (Becton Dickinson) (Bulmer *et al.* 1986) together with the peroxidase-anti-peroxidase technique. Sections were dewaxed and endogenous peroxidase was removed as described above. Subsequently the sections were trypsinised for 10 min at 37°C (0.1% trypsin in 0.1% $CaCl_2$ at pH 7.8). The slides were immersed in cold running tap water for 10 min to remove all the trypsin solution, and then washed in PBS. Mouse monoclonal antibody to CAM 5.2 was applied at a dilution of 1/10 PBS and the slides were left overnight at 4°C. Subsequently they were washed in PBS and rabbit antiserum to mouse immunoglobulins (DAKO) was applied at 1/50 PBS for 30 min. After washing, mouse peroxidase-anti-peroxidase (DAKO) was applied at 1/50 PBS for 30 min. The peroxidase was localized using DAB as the substrate as above. For control sections, CAM 5.2 was replaced by normal mouse ascites.

Statistical analysis

The immunocytochemical staining was compared using χ^2 analysis. The patient characteristics were compared using the Student's *t*-test for age, gestation and birthweight centile, and χ^2 analysis for parity and mode of delivery. The Spearman rank test with correction for ties was used to assess correlation with staining being ranked 1, 2 or 3 according to minimal, moderate and heavy, respectively.

Results

When placental bed sections were stained with

normal mouse ascites as a negative control, there were no reaction, but with the anti-cytokeratin monoclonal antibody, CAM 5.2, both the extravillous trophoblast and endometrial glands were stained. The glands showed typical morphology, and the remaining stained cells, some of which were multinucleated, were identified as trophoblast. Several placental bed biopsies were discarded as it was judged that these did not contain trophoblast and we could not be certain that this material originated from the placental site. Of the 26 placental bed specimens collected, 11 contained trophoblast (5 normal pregnancies and 6 with PIH).

In most cases, sections from the placenta contained not only villi and the subchorionic plate but also some decidual tissue. When stained with antiserum to neutrophil elastase, the brown reaction product was localized exclusively to neutrophils, some of which were sectioned to illustrate their round profile and lobed nuclei. Fetal mesenchymal cells, the villous and extravillous trophoblast, endothelial cells, and decidual cells showed no reaction product. Sections of placental bed also contained decidual tissue, together with myometrium. When stained for elastase, only neutrophils were positive, whilst extravillous trophoblast and all other maternal cells of the myometrium remained unstained. Control sections in which normal sheep serum was employed showed no staining.

Neutrophils could be located both in the lumen of the fetal blood vessels within the villi, and also in the intervillous space. In addition, neutrophils were identified in extravascular locations. On careful examination of serial sections stained with haematoxylin and eosin, it was found that neutrophils, which were often stellate or fusiform, were located within areas of fibrin. These fibrin areas were found in the subchorionic plate, around the villi (perivillous fibrin) (Fig. 1a), and in the decidua (Fig. 1b). In this region, the fibrin areas were located among extravillous trophoblast and decidual cells, and in the walls of maternal vessels. Examination of placental bed sections confirmed that neutrophils were present in fibrin in the decidual region, but they were not present in the myometrium.

Staining was analysed by one of us (BHB) who was unaware of the patient's diagnosis. Neutrophils in fetal vessels and the intervillous space were not included in the assessment. Similarly, neutrophils that were not totally embedded in

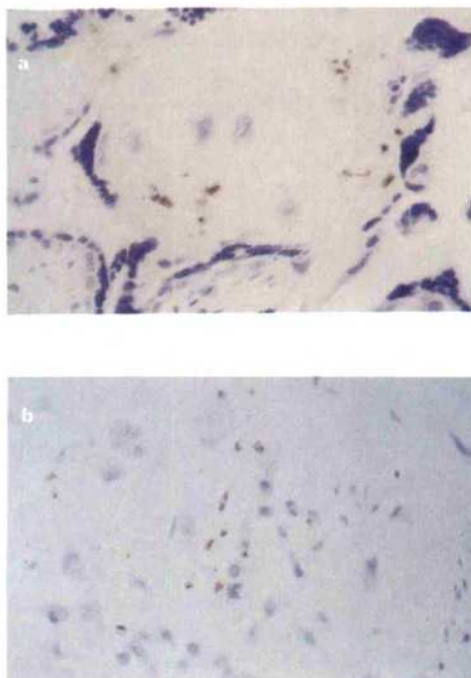


Fig. 1. Sections of placenta from patients with pregnancy-induced hypertension (PIH) stained for neutrophil elastase. Positive cells are coloured brown. In (a) neutrophils are located in perivillous fibrin whilst the mesenchyme and syncytiotrophoblast of the adjacent villi are negative. $\times 40$. In (b) elastase positive neutrophils can be identified in the decidua. $\times 320$.

fibrin were excluded from the enumeration, since they could represent vascular neutrophils that had simply adhered to adjacent tissue during section preparation. From sections of placenta, the numbers of positive cells in the subchorionic plate and perivillous fibrin were estimated subjectively as minimal (or absent), moderate or heavy. The results are tabulated in Table 2.

Decidual tissue was available from 40 patients (18 normal, 22 with PIH). In most cases, decidual tissue was present on sections of placenta only (13 normal, 16 with PIH) but in some cases it was present on sections of placental bed only (1 normal, 4 with PIH). In six women decidual tissue was present on both sections of placenta and placental bed (4 normal, 2 with PIH) and for these an average value of the number of elastase positive cells was calculated. The results are tabulated in Table 2. There was a significant difference between the groups on analysis of the decidual content of elastase positive neutrophils ($P < 0.02$). There was no significant correlation

between decidual elastase staining and birth-weight centile ($r = -0.32$; $P > 0.05$), platelets ($r = -0.33$; $P > 0.05$), or proteinuria ($r = 0.41$; $P > 0.05$), but there was a significant correlation with plasma urate ($r = 0.68$; $P < 0.02$).

Discussion

In this study, we have used an immunocytochemical technique to localize neutrophil elastase in the placenta, decidua and myometrium from normal and PIH pregnancies. Elastase positive neutrophils were located within fetal blood vessels and the intervillous space and these cells tended to be round, often illustrating the multilobular morphology of their nuclei. In addition, neutrophils could also be identified in extravascular sites. These cells seldom showed typical morphological features and would be difficult to delineate on sections stained with conventional histological methods.

The results have illustrated that even in normal pregnancies there is some accumulation of neutrophils in the placenta and decidua and if there is a degree of cell activation this finding may explain why plasma elastase levels are

Table 2. Presence of elastase positive neutrophils in normal pregnancies (N) and in pregnancies complicated by pregnancy-induced hypertension (PIH)¹

	Total	Minimal	Moderate	Heavy
Subchorionic plate				
N	22 ²	13	5	4
PIH	28	18	6	4
Perivillous fibrin				
N	23	20	2	1
PIH	28	16	7	5 ³
Decidua ⁴				
N	18	13	4	1
PIH	22	6	8	8

¹ Two specimens (1 normal and 1 PIH) showed staining within the arterial wall in the subchorionic plate. Positive cells were confined to the vessels, with the mesenchyme of the subchorionic plate showing no positive cells.

² On sections from one normal placenta, the subchorionic plate was absent.

³ One specimen showed excessive accumulation of neutrophils in the villi just underneath the syncytiotrophoblast. No neutrophils were present in the mesenchyme.

⁴ The normal and PIH groups were significantly different for elastase positive neutrophils in decidua $P < 0.02$, χ^2 analysis.

higher in women with normal pregnancies than in normal non-pregnant women (Greer *et al.* 1989). In placentas from pregnancies with PIH, there was no significant difference in the number of neutrophils in the subchorionic plate and perivillous fibrin when compared with normal placentas. However, the number of neutrophils in the decidua was significantly greater in the PIH group than in the normal group.

It is likely that these extravascular neutrophils found in both normal and PIH pregnancies are of maternal origin. Although elastase positive neutrophils were located in fetal vessels, these are likely to represent normal fetal neutrophils in the circulation. Neutrophils were not located in the fetal mesenchyme of the villi, and it therefore seems unlikely that any of these cells migrate through the fetal tissues towards areas of fibrin.

The reason behind the accumulation of elastase positive neutrophils in the decidua of the placental site in PIH is unclear. This may represent a secondary phenomenon consequent upon tissue ischaemia due to an inadequate maternal vascular response to placentation (Khong *et al.* 1986) which may provoke many of the pathological changes seen in PIH (Fox 1987), or may be triggered by immunological mechanisms which have been implicated in the aetiology of this disorder (Stirrat, 1987). Regardless of the mechanism, activation of these neutrophils is likely to contribute to the tissue and vascular damage seen in PIH, just as they contribute to immunologically and ischaemia mediated damage in the non-pregnant (Harlan 1987). With either possibility, however, we feel that neutrophil activation would represent a secondary rather than a primary phenomenon in the pathophysiology of the vascular damage seen in PIH. There was a direct correlation between plasma urate and decidual elastase suggesting that elastase staining parallels disease severity as judged by plasma urate. McFadyen *et al.* (1986) noted previously that raised plasma urate was related to maternal vascular damage judged histologically on placental bed biopsies. This would be in keeping with our hypothesis that neutrophil elastase may contribute to the vascular damage in the placental bed.

The results of this study suggest that the neutrophil activation, which has been reported previously in terms of elevated maternal plasma levels (Greer *et al.* 1989), may be localized, at least in part, in the decidual region of the pla-

cental site. The release of neutrophil elastase, together with other mediators from the azurophilic granules, could contribute to the vascular damage evident in the decidual region in PIH.

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Unfavourable pregnancy outcome associated with congenital protein C deficiency. Case reports

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Case reports

Patient 1

A 36-year-old woman was referred in 1988 after giving birth to her second child, a severely growth-retarded infant weighing 1880 g at term. The placenta showed massive infarction, occupying 80% of its volume. Maternal hemostasis was investigated for evidence of anomalies such as lupus anticoagulant. Protein C activity was measured on a chromogenic substrate (Chromotime, Behring) and by a commercial ELISA method (Asserachrom Protein C, Diagnostica Stago). Protein C levels were 43% of the normal. There was no personal or family history of thrombosis, but she had Hashimoto's thyroiditis. Her obstetric history included one first trimester miscarriage and, in 1985, she had given birth uneventfully to a 3250 g boy at term. In 1990, following the diagnosis of protein C deficiency, she was followed in our department during her third ongoing pregnancy. Low molecular weight heparin (Fraxiparine, Choay, France) was administered at 7500 U, one subcutaneous injection daily, from the fourth month until the post partum period. The course of pregnancy was uneventful, and at 39 weeks she gave birth to a healthy boy weighing 3605 g. The placenta contained several small ischaemic lesions.

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Patient 2

This woman's first ongoing pregnancy, in 1981, at the age of 24, was suddenly complicated by placental abruption at 30 weeks. She was delivered by emergency caesarean section, but the infant died 2 days after the birth. She had had two elective abortions; she had no previous medical history. In 1983, she presented with generalized tonic-clonic convulsions. Computerized tomography of the brain showed two hypodense lesions, whose localization did not suggest a vascular topography. The aetiology could not be determined. While she was in the department of neurosurgery, calf vein thrombosis occurred, and this was treated by standard heparin therapy. There was no family history of thromboembolic disease. In 1984, during the first trimester of her second ongoing pregnancy, convulsions recurred and the brain scan showed the same unsystematized lesions as before. Low molecular weight heparin (Fraxiparine) was administered as one 7500 U injection daily from 32 weeks until the post-partum period. A healthy 2700 g infant was born at 38 weeks gestation by caesarean section. Pathological examination of the placenta was not performed. Protein C deficiency, at 47% of the normal adult level, was discovered (using two techniques described for the first patient) in January, 1985. She was referred to us in 1989 in a further pregnancy. Low molecular weight heparin was administered at 7500 U daily from 23 weeks until 1 month post partum. Prenatal course was uneventful. A healthy 2600 g male infant was born by caesarean section at 38 weeks gestation. The placenta contained numerous small foci of ischaemic necrosis along the basal plate.

Discussion

Protein C deficiency is transmitted as an autosomal dominant trait. Its association with

hereditary thrombo-embolic disease was first reported by Griffin *et al.* (1981). The prevalence of the heterozygous form, which is estimated at 1 in 16000 in the general population, is 8% in patients with deep venous thrombosis occurring before the age of 40 (Horrelou *et al.* 1985). About 50% of patients with protein C deficiency suffer one or more episodes of thrombo-embolism before reaching 30 years of age (Vogel *et al.* 1989). Protein C is a vitamin K-dependent physiological inhibitor of coagulation, which was characterized by Stenflo (1976). It is activated by thrombin in the presence of its receptor, thrombomodulin, expressed on the surface of vascular endothelial cells, and of protein S. It is involved in inactivating factors Va (proaccelerin) and VIIIa (antihaemophilic A), thereby slowing the activation of factor X by factor IXa, and subsequently thrombin formation (Kisiel *et al.* 1979). It also appears to be involved in the inactivation of fibrinolysis.

Protein C deficiency has been shown to be associated with thrombo-embolism during pregnancy and the post partum period, during which the risk of deep venous thrombosis is increased, even in unaffected women, because of haemodynamic and haemostatic changes. In a recent study of 36 women with protein C deficiency, Conard *et al.* (1990) found an incidence of thrombosis of 7% during pregnancy and 19% during the post partum period. Past or present pregnancy outcome for these women was not mentioned.

Two publications have reported gestational complications in women with protein C deficiency. Brenner *et al.* (1987) reported a 22-year-old woman who developed severe pre-eclampsia in three successive pregnancies. The first was terminated by emergency caesarean section at 26 weeks. Birthweight and placental pathology were not reported. The infant died on day 10. During her second pregnancy, fetal death occurred at 36 weeks (birthweight not reported). Pathology showed extensive placental infarction. Deep vein thrombosis occurred in the post partum period. Deep vein thrombosis recurred during the first trimester of her third pregnancy. Diagnosis of protein C deficiency at 55 U/dl was made at this time. Heparin therapy was begun at 7500 U twice daily. The course of pregnancy was marked by intrauterine growth retardation with severe pre-eclampsia at 35 weeks leading to the birth of a 1750 g infant, who survived. The placenta showed extensive infarction.

Lamvik *et al.* (1987) reported a 19-year-old woman who had two successive fetal deaths. During her first pregnancy, fetal death occurred suddenly at 32 weeks, without an apparent cause. Birthweight was not reported. A large infarct covered two-thirds of the placenta. In the post partum, deep vein thrombosis and pulmonary embolism occurred, leading to the diagnosis of protein C deficiency. During her second pregnancy, standard heparin (5000 U three times daily) was prescribed, but treatment was not maintained consistently. Fetal death occurred suddenly at 27 weeks (birthweight not reported). Placental infarction was again noted.

The common feature among the above four reports, concerning a total of 11 pregnancies, appears to be compromise of the uteroplacental circulation, which can be responsible for intrauterine growth retardation, pre-eclampsia, placental abruption and/or fetal death. Ischaemic lesions of the placenta were found in nearly all cases. It should be noted that one of our patients had massive placental infarction and a severely growth-retarded fetus without ever having deep vein thrombosis and that the three other women experienced gestational complications before the occurrence of thrombophlebitis.

Whether protein C deficiency is responsible for these gestational complications can at most be suspected. If such a relation were to be confirmed, there would be the prospect of preventive therapy in affected patients. However, although anticoagulant therapy appears to be effective in preventing thromboembolic complications during pregnancy and the post partum, its effect on pregnancy outcome is unknown. Among pregnancies complicated by placental ischaemia, the cause is not found in most cases. Coagulation abnormalities, such as the 'lupus anticoagulant' are infrequent. More systematic exploration for protein C deficiency may be considered to determine whether or not it is a risk factor for placental ischaemia.

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emphasis was placed on drinking water consumption, including tea and coffee and the intake of supplements. The questionnaire also served as a basis for the interview when, for example, slices of bread reported in the questionnaire were specified by type of bread, thickness of each slice and amount and type of spread. The interview further provided detailed information about the composition of cooked meals: type and intake frequency of meat or fish and additional ingredients such as potatoes, rice, pasta, vegetables and sauce. Photographs of models were used to estimate the size of portions eaten. The results of the questionnaire and the interviews were checked by an experienced nutritionist and when there were uncertainties the participants were contacted for further information. Energy and nutrient intake was calculated using a national food data base (DANKOST). For estimates of intake of magnesium from water, information on the content of mineral salts in the water in the area was provided by the municipal administration. Magnesium content in the water was 9 mg per litre.

In addition the self-questionnaire gave information about education, occupation, income, size of household, smoking habits, and physical activity.

Serum and tissue samples

Blood samples were collected in the 30th week gestation and again in the 37th week to measure serum magnesium by atomic absorption. In a small subpopulation muscle biopsies were obtained from the vastus lateralis muscle in the 30th, the 33rd or the 37th week gestation for later analysis of electrolyte content. Biopsy specimens of the vastus lateralis muscle were taken using a Bergström needle under local anaesthesia. One biopsy yielded three or four specimens of about 20 mg wet weight. These were immediately weighed, frozen, and stored in sealed plastic tubes until measurement could be made. In some women delivered by caesarean section a biopsy from the abdominal rectus muscle and the uterus was taken. This biopsy was immediately cut into pieces of about 20 mg each, which were then prepared as described for the vastus lateralis biopsies. For the determination of magnesium, samples were homogenized in 2 ml of trichloroacetic acid (300 mmol/l) using an Ultra-turrax homogenizer, centrifuged for 10 min at 2000 rev/min, and the clear super-

natant taken for further dilution with 2 volumes of redistilled water. This dilution was used for determination of the magnesium content by atomic absorption (Perkin Elmer 5000, wavelength 285.2 nm). The details of this procedure for magnesium determination have been described by Dørup *et al.* (1988a).

Obstetric and neonatal data

After delivery, data concerning previous pregnancies, the course of the current pregnancy and delivery, maternal weight and weight gain, and the course of the neonatal period were collected from the midwifery and hospital records and stored in a computer.

Definitions

Pre-eclampsia. Blood pressure $\geq 140/95$ mmHg after 20 weeks gestation with proteinuria ≥ 0.3 g/l in women previously normotensive.

Small for gestational age (SGA). Birthweight for gestational age below the 10th centile. The expected weight for gestational weight were calculated according to the formula: $\alpha + \beta(\text{GA}-280)$ (Secher *et al.* 1986), where GA is the gestational age in days at birth, α is the expected weight at term (3437 g for boys and 3322 g for girls); and β is the weight gain per day (28.72 g for boys and 27.27 g for girls).

Preterm labour. Spontaneous onset of labour of ≤ 259 days gestation without pre-eclampsia or a SGA-infant.

Statistics

The association between magnesium intake and mean birthweight was adjusted for possible confounding factors by multiple linear regression. χ^2 tests were used for bivariate analysis, and analysis of variance or *t*-test, when appropriate, for comparisons of group means. χ^2 -test for linear trend was used for testing trend in group proportions. A significance level of 5% was chosen.

Results

General characteristics

No differences in age, parity, gestational age, birthweight, and frequency of certain pathological pregnancies were found between the study population and the women who did not want to take part in the study. In both groups the occur-

rence of pre-eclampsia and preterm labour was 1.3–1.4% and 2.4%, respectively, and about 6.5% gave birth to SGA infants (Table I). Thus, selection bias concerning pregnancy outcome did not seem to be introduced by the defection from the eligible population.

A relatively large proportion of the study population consisted of well-educated women. Thus, 83 (9%) had an academic training and a further 309 (32%) had gone through 13 to 16 years of education. 151 (16%) were students, mostly at the university.

Overall 66% were non-smokers, only 1% smoked more than 20 cigarettes/day, 23% smoked less than 10/day, and 10% smoked between 10 and 20 cigarettes daily.

Nutrient intake

In the whole population under investigation the mean magnesium intake was as high as 445 (95% range 256 to 631) mg per day, which included intake through food, water and other nutritional supplements. Only 81 women took supplements which contained magnesium, each 100 mg magnesium per day. The mean magnesium intake among the subgroups of women who later developed pre-eclampsia, gave birth to a SGA-infant, or had a preterm labour was 446 (SD 89), 449 (SD 109), and 473 (SD 106) mg per day, respectively.

The intake of specific nutrients is often highly correlated to total energy intake. Nutrient density i.e., nutrient intake in relation to total caloric intake is therefore the most relevant

measure when disease is considered to be associated with the intake of specific nutrients (Willet 1989). In the present study magnesium intake was highly correlated with energy intake ($r^2 = 0.8$). Figure 1(a) compares magnesium density (mg magnesium per 1000 kcal per day) between women with a normal pregnancy and those with pathology (pre-eclampsia, SGA infants or preterm labour). The mean value was

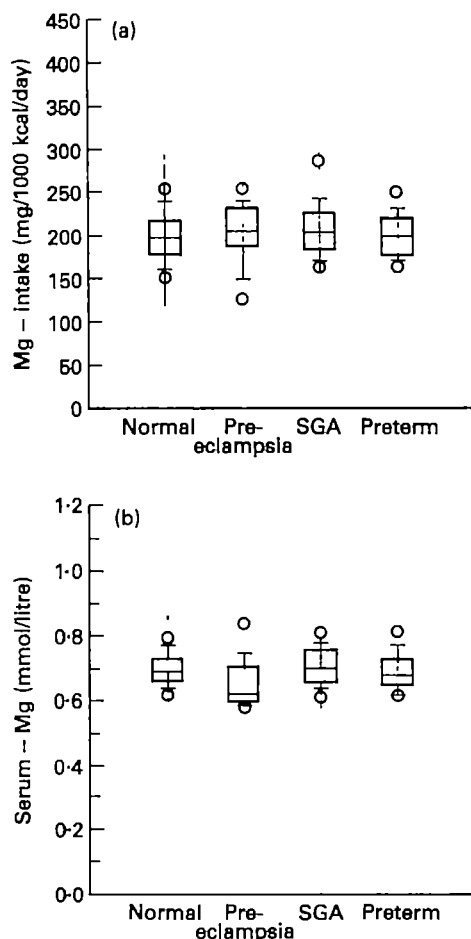


Table 1. Clinical data for the study group and for those who refused to participate in the study

	Participants (<i>n</i> = 965)	Non-participants (<i>n</i> = 212)
Age (years)	28.7 (18–45)	28.5 (16–42)
Parity		
1	556 (57.6)	97 (45.8)
2	306 (31.7)	70 (33.0)
3	103 (10.6)	45 (21.2)
Pre-eclampsia	13 (1.3)	3 (1.4)
SGA-infants	63 (6.5)	14 (6.6)
Preterm labour	23 (2.4)	5 (2.4)
Birthweight (g)	3500 (1155–5720)	3500 (820–4970)
Gestational age (days)	284 (214–316)	282 (209–310)

Results are median (range) or *n*(%) values as appropriate.

Fig. 1. Magnesium intake as (a) mg magnesium per 1000 kcal per day and (b) as serum magnesium in groups according to pregnancy outcome. Information on the magnesium intake and blood samples were obtained in the 30th week gestation before the disorders had developed. The horizontal lines of the plot mark the 10th, 25th, 50th, 75th and 90th centiles of the intake. The box encompasses the 25th through 75th centiles. The circles represent the 5th and 95th centiles. There were no significant differences between the groups.

Table 2. Distribution of some maternal and infant characteristics by level of magnesium intake

	Magnesium-intake (mg/1000 kcal/day, quintiles)					
	(n)	<173 (n = 193) (%)	173-190 (n = 193) (%)	190-206 (n = 193) (%)	206-223 (n = 193) (%)	>223 (n = 193) (%)
Age (years)						
<20	6	50	17	33	—	—
20-24	141	28	22	16	15	19
25-29	441	22	19	21	20	18
30-34	284	15	19	21	22	24
≥35	89	12	28	15	24	21
Parity						
1	556	18	19	22	20	21
2	306	24	22	16	21	17
3+	103	17	22	19	18	23
Education (years)						
≤12	355	25	21	20	17	17
13-16	309	17	20	20	20	23
≥17	83	18	22	22	22	17
Student	151	15	19	19	24	24
Missing	67	27	13	19	25	15
Cigarettes (daily)						
0	633	21	19	21	19	19
1-10	226	16	24	18	25	19
10-20	95	28	18	17	12	25
>20	11	9	—	27	27	36
Weight gain (kg) mean (SD)		14(6)	14(6)	14(5)	14(5)	14(5)
Prepregnancy weight (kg) mean (SD)		60(10)	61(11)	60(10)	60(8)	61(10)
Height (m) mean (SD)		1.7(0.1)	1.7(0.1)	1.7(0.1)	1.7(0.1)	1.7(0.1)
Birthweight (g) mean (SD)		3543 (511)	3579 (563)	3493 (551)	3471 (544)	3410 (470)
Pre-eclampsia	13	15	8	31	15	31
SGA	63	16	13	25	21	25
Preterm labour	23	17	17	22	22	22

about 200 mg per 1000 kcal per day and was similar in all groups. As indicated the distribution of the magnesium density was almost the same in all groups.

Table 2 describes the distribution of some maternal and fetal characteristics by level of quintiles of the magnesium density. The proportions of pathological pregnancies in the groups of magnesium intake showed no difference. Significantly more women below 20 years of age had low magnesium intake compared to the rest of the population, whereas parity and smoking habits seemed to be without influence on the magnesium intake. Likewise the intake of magnesium was independent of educational status. Prepregnancy weight and height, weight gain during pregnancy and birthweight were similar in all groups. As shown in Table 3, the propor-

tions of pre-eclampsia, SGA-infants or preterm labour did not differ significantly between the educational groups. Smoking involved an increasing proportion of SGA-infants and 17.9% of those who smoked 10 to 20 cigarettes per day gave birth to a SGA-infant compared with 3.9% among non-smokers.

The intake of total energy, protein, carbohydrate, fat and nutrient fibre was closely similar in the groups irrespective of pregnancy outcome. Total energy intake was around 2275 kcal/day (SD 540). The intake of fat was only about 35 g/1000 kcal, the carbohydrate about 125 g/1000 kcal, and protein about 41 g/1000 kcal in all groups. Thus, in all groups the consumption of protein, carbohydrate and fat accounted for about 16%, 50% and 32% of total energy intake, respectively. The intake of nutri-

Table 3. Pregnancy outcome related to some maternal characteristics

	<i>n</i>	Pre-eclampsia (%)	SGA (%)	Preterm labour (%)
Age (years)				
<20	6	—	—	16.7
20–24	141	1.4	9.9	1.4
25–29	441	1.1	5.2	3.4
30–34	284	2.1	7.7	1.4
≥35	89	—	4.5	1.1
Parity				
1	556	1.4	7.2	2.9
2	306	1.6	5.2	1.6
3+	103	—	6.8	1.9
Education (years)				
≤12	355	1.4	6.8	2.3
13–16	309	1.6	6.5	1.6
≥17	83	1.2	4.8	2.4
Student	151	0.7	9.3	4.6
Missing	67	1.5	1.5	1.5
Cigarettes (daily)				
0	633	1.4	3.9	2.5
1–10	226	0.9	9.3	2.7
10–20	95	2.1	17.9	1.1
>20	11	—	—	—

ent fibre was found to be about 27 g (SD 8) per day in all groups and about 14 g/1000 kcal per day.

Birthweight was around 4% lower among the women with high magnesium intake (Table 2). Analysis of variance showed that this difference was significant at the 2% level. However, the negative influence of magnesium intake on birthweight was not significant in a multiple linear regression model, which showed that

birthweight was significantly reduced only by low gestational age, low parity, smoking, low maternal prepregnant weight and height, and low weight gain during pregnancy. Only women, who were delivered after 37 weeks were included in this regression model (Table 4).

Serum and tissue determination

A similar mean level of serum magnesium of

Table 4. Effects of magnesium intake and other factors on mean birthweight in term deliveries according to a multiple linear regression model

	Regression coefficient	95% CI	<i>P</i>
Magnesium intake*	−0.7	−1.5 to 0.2	0.13
Prepregnant weight*	8.8	5.4 to 12	< 0.0001
Maternal height*	13	7.6 to 18	< 0.0001
Weightgain*	20	15 to 26	< 0.0001
Smoking†	−165	−222 to −105	< 0.0001
Parity‡	107	48 to 166	0.0004
Age§	−1.1	−4.0 to 1.9	0.49
Gestational age (weeks)*	132	109 to 155	< 0.0001

* Continuous variable, † Smoking vs non-smoking, ‡ Nulliparous vs parous, § Continuous variable 1–5. According to this model, birthweight (g) can be expressed as: $-4696 + 8.8 \times \text{prepregnant weight (in kg)} + 13 \times \text{maternal height (in cm)} + 20 \times \text{weight gain (in kg)} - 165 \text{ (for smoking)} + 107 \text{ (for multipara)} + 132 \times \text{gestational age (in weeks)}$, i.e., a non-smoking nullipara who is 170 cm of height, weighing 60 kg, gained 10 kg during pregnancy and delivered after 40 weeks of gestation is expected to give birth to an infant of about 3500 g.

Table 5. Magnesium and sodium concentration ($\mu\text{mol/g}$ wet weight) in biopsies from abdominal rectus muscle and uterus from pregnant women

	Rectus ABD		Uterus
	Mg	Na	Mg
Normal pregnant (<i>n</i> = 14)	7.7 (0.2)	33.5 (1.5)	3.7 (0.1)
Pre-eclampsia (<i>n</i> = 12)	7.1 (0.3)	37.4 (2.0)	3.7 (0.2)
SGA-infant (<i>n</i> = 5)	7.6 (0.3) <i>P</i> = 0.24	31.7 (2.1) <i>P</i> = 0.14	3.7 (0.3) <i>P</i> = 0.99

Results are mean (SEM) values.

0.7 mmol/l was found at 30 and 37 weeks gestation. Figure 1(b) shows the distribution of serum magnesium values at 30 weeks among the groups with different pregnancy outcome. In the pre-eclamptic group, mean serum magnesium was 6% lower than in the normal pregnancy group, but the difference was not significant. There was no correlation between the magnesium intake and the level of serum magnesium.

We did not find any difference in magnesium intake or serum magnesium between the group of normal pregnant women and those women who later developed pre-eclampsia or gave birth to a SGA infant. Therefore, we subsequently compared the magnesium status at delivery in normal pregnant women and in women with pre-eclampsia or an SGA infant by another approach. It has been shown previously, that the magnesium content in skeletal muscle serves as a marker of magnesium status (Dyckner & Wester 1979; Dørup *et al.* 1988b). From Table 5 it appears that the magnesium content at biopsies from the abdominal rectus muscle taken during caesarean section was similar and was unrelated to pregnancy outcome. The value was slightly lower in the pre-eclamptic group, but the difference was probably due to an increase in extracellular water since a parallel increase in sodium content was observed in these biopsies.

To eliminate the possibility that a regional magnesium deficiency could be present in the pre-eclamptic pregnancies or in pregnancies with an SGA-infant, we also determined the magnesium content of myometrial biopsies. There were no differences between the groups. (Table 5).

The duration of pregnancy was longer in the women with normal pregnancies than in those with pathology. If the magnesium content in the

muscles decreases as gestation continues, this might obscure a possible difference in the magnesium content between the normal and the pathological pregnancies. Therefore, the magnesium content of biopsies from the vastus lateralis muscle of normal pregnant women taken in the 30th, 33rd or 37th week gestation was determined. The magnesium content was 6.4 (SE 0.2, *n* = 13), 6.4 (SE 0.6, *n* = 7), and 6.5 (SE 0.6, *n* = 7) $\mu\text{mol/g}$ wet weight, respectively. The corresponding sodium content was 58.3 (SE 2.6), 60.0 (SE 3.3), and 67.7 (SE 3.5) $\mu\text{mol/g}$ wet weight. Analysis of variance showed that the difference in sodium content was not significant (*P* = 0.11). Although the magnesium concentration in these biopsies was lower than in biopsies from the rectus abdominal muscle due to more extracellular water (sodium concentration higher), the discrepancy in length of pregnancy should therefore not hinder the comparison of magnesium content between the women with pre-eclampsia or SGA-infants and the normal pregnant women.

Discussion

The method of estimating the dietary intake of nutrients provided information on the usual diet during the last 3 months, and was able to assess the nutrient intake at group level. This made it possible to compare the distribution of nutrient intake in groups according to various pregnancy outcomes.

The estimate of the mean magnesium intake of 445 mg per day (95% range 256 mg to 631 mg) was high when compared with estimates in previous surveys using weighed dietary records. Thus, Doyle *et al.* (1989) and Black *et al.* (1986) reported an intake of magnesium by pregnant

women of about 250 mg and 300 mg/day, respectively. In a survey conducted by the Danish National Food Agency (Haraldsdottir *et al.* 1986), using a history of diet method, the average magnesium intake among non-pregnant women was estimated to 289 mg/day (95% range 174 to 465 mg). When less comprehensive methods, such as 24-h recall, were employed the mean magnesium intake of pregnant women was estimated to be from 184 mg to 316 mg/day (Endress *et al.* 1981; Lillen *et al.* 1982; Sibai 1989). When corrected for energy intake, the estimate of magnesium intake was higher in the present study than in the previous investigations. Whereas the estimates of total energy and protein intake in the present study were in good agreement, the estimate of total fat intake were well below and the estimate of carbohydrate intake well above those of many other dietary surveys of pregnant women (Black *et al.* 1986; Moser *et al.* 1983; Durnin *et al.* 1987; Simmer *et al.* 1987; Forsum *et al.* 1988). Thus, on average 32% of total energy intake came from fat and 50% from intake of carbohydrate. A low fat diet has a higher nutrient density than a high fat diet and this may explain the relatively high magnesium density found in our study. The dietary fibre intake was 27 g/day. This is about 30% higher than that observed previously among English pregnant women (Black *et al.* 1986) and among non-pregnant Danish women (Haraldsdottir *et al.* 1986) and provides further evidence that the diet of the present population was of high quality and this implies a high magnesium content.

Serum magnesium could not serve as a biochemical validation of the magnesium intake, since no correlation between these variables was found. This was in agreement with the results of Moser (1983), who was not able to find any correlation between serum magnesium and the magnesium intake assessed by the method of analyzing composite duplicates of the food ingested. Serum magnesium seems to be regulated within a narrow range, primarily by the kidneys which effectively conserve magnesium when intake is low (Shills 1969; Flink 1980). Thus, serum magnesium does not provide a suitable index for the assessment of magnesium status even at group level and it is not surprising that no differences between the groups were found in the present study nor in the study of Boston *et al.* (1989), who compared the serum magnesium between women with pregnancy-

induced hypertension and those with normal pregnancies.

In the present study average magnesium intake was similar in all groups of pregnant women considered. Furthermore, the proportion of women with low magnesium intake did not differ between the normal and the pathological pregnancies. Thus, pre-eclampsia or SGA infants were not associated with low magnesium intake. Such an association has been suggested previously (Altura *et al.* 1983; Conradt *et al.* 1984) on the basis of indirect evidence. In the study of Conradt (1984) magnesium intake was assessed after the diagnosis of the pregnancy disorder, and Altura *et al.* (1983) based their suggestions on experiments on isolated human umbilical vessels, which showed a contraction response when magnesium was omitted from the extracellular medium. A Swiss double-blind study of magnesium supplementation (Spätling & Spätling 1988) found that a magnesium supplement during pregnancy reduced the number of low-birthweight infants. This was due to fewer preterm labours, but this finding should be questioned, since the placebo and treatment groups were not strictly comparable as there was a higher number with antepartum haemorrhage in the placebo group. In another double blind study (Sibai *et al.* 1989), magnesium supplementation did not reduce the occurrence of either pre-eclampsia or SGA-infants.

In a steady state the renal excretion of magnesium reflects the intake or more precisely the amount of magnesium absorbed. When not in steady state, a very low excretion can be ascribed to magnesium deficiency. In the cross-sectional study of Roelofson *et al.* (1988) the renal excretion of magnesium was measured in normal pregnant women and in women with pre-eclampsia with or without fetal growth retardation; no differences could be detected. This observation suggests that pre-eclampsia or intra-uterine growth retardation are not associated with magnesium deficiency, and this is in agreement with the present results. It has been shown previously that measurements of magnesium content in skeletal muscle is a suitable way to assess magnesium status (Dyckner & Wester 1979; Dørup *et al.* 1988b). The magnesium content of the abdominal rectus muscle was similar in all groups of pregnant women considered in the present study. The magnesium content was about 10% lower than measured in vastus lateralis and rectus abdominalis muscle of non-

pregnant subjects (Dyckner & Wester 1979; Dørup *et al.* 1988 a, b). This is in accordance with the results of Cheek *et al.* (1985), who demonstrated that the lower content of intracellular electrolytes in the abdominal rectus muscle of pregnant women was due to an increase in extracellular water. Thus, the slight, but non-significant decrease in muscle magnesium among the pre-eclamptic women can be explained by water retention as reflected by the raised sodium content in the muscle biopsies (Dørup, *et al.* 1988a).

Neither magnesium intake nor protein, carbohydrate or total fat intake were correlated with birthweight, but in agreement with other studies (Martin & Bracken 1987; Brooke *et al.* 1989; Abrams *et al.* 1989), smoking, maternal prepregnancy weight and height, weight gain during pregnancy and parity influenced birthweight in the present investigation.

In conclusion, in the population studied there was no association between pre-eclampsia SGA-infants or preterm labour and low intake of magnesium when compared with the intake in normal pregnant women. Since assessment of intakes does not necessarily reflect the body status of the element in question, a cross-sectional study to assess magnesium status was undertaken, and the results did not support the idea that pre-eclampsia, fetal growth retardation or preterm labour should be characterized by magnesium deficiency. Although the method used for estimating the dietary intake was mainly appropriate at group level, the intake of magnesium in the current population seems to be adequate. Taken together, routine magnesium supplementation during pregnancy is not to be recommended in populations of relative good socio-economic status.

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Fetal middle cerebral artery flow velocity waveforms—a terminal pattern. Case report

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Case report

A 32-year-old woman was referred at 22 weeks gestation in her second pregnancy with proteinuric pre-eclampsia superimposed on essential hypertension and intrauterine growth retardation (IUGR). Her first pregnancy 7 years previously by the same partner was uneventful and she had a full term normal delivery of a boy weighing 3600 g.

In 1988, she was diagnosed as having essential hypertension and was treated with enalapril and bendrofluazide. Early in the first trimester of the present pregnancy, these drugs were substituted with methyldopa. At 21 weeks gestation she developed proteinuria and worsening hypertension and an ultrasound examination revealed symmetrical IUGR without any fetal anomaly.

At admission, her blood pressure was 150/100 mmHg and she was asymptomatic. There was pitting oedema of both lower limbs and her reflexes were normal. The symphysio-fundal height was only 16 cm. Her uric acid level was 289 $\mu\text{mol/l}$ and she had significant proteinuria of 8 g in 24 h. The earlier ultrasound findings were confirmed and the fetal head and abdominal circumferences were below the 2.5-centile of our reference range for gestational age. Fetal blood sampling revealed a normal karyotype (46 XX). Because of the extreme immaturity and severe IUGR, the fetus was considered to be pre-viable and fetal well-being was not monitored. As part of a research protocol, however, the middle

cerebral artery flow velocity waveform (FVW) was studied serially.

These FVWs were obtained using an Ultra-mark V pulsed Doppler system (3.5 MHz curvilinear transducer, high pass filter 50 Hz). Although this system did not have colour flow imaging, using the technique and landmarks previously described (Vyas *et al.* 1990a), the middle cerebral artery was easily identified and insonated. All measurements were performed by the same operator (RC) with the woman in the semi recumbent position and in the absence of gross fetal body or breathing movements. Care was also taken to apply minimal pressure to the maternal abdomen with the transducer. The pulsatility index (PI) was calculated over at least 3 consecutive cardiac cycles. The intra-observer correlation coefficient for the measurement of PI of FVWs from the fetal middle cerebral artery had been determined previously by performing four consecutive examinations on five appropriate-for-gestational age fetuses within a 1 h period ($r = 0.89$, $P < 0.001$).

Maternal hypertension was controlled with methyldopa and nifedipine but at 24 weeks gestation the fetus died *in-utero*. Starting 14 days before fetal death, the middle cerebral artery was insonated on four different occasions a few days apart. The PI value obtained at each examination was plotted against the normal curves published previously by Vyas *et al.* (1990a). A progressive fall in the PI was followed by an increased value on the last measurement taken 12 h before fetal death (Fig. 1). Delivery was expedited with prostaglandin pessaries and oxytocin infusion and a stillborn female weighing 400 g was delivered vaginally. Autopsy did not reveal any fetal abnormality. Detailed examination of the brain revealed changes of maceration with evidence of terminal hypoxia. There was no evidence of haemorrhage.

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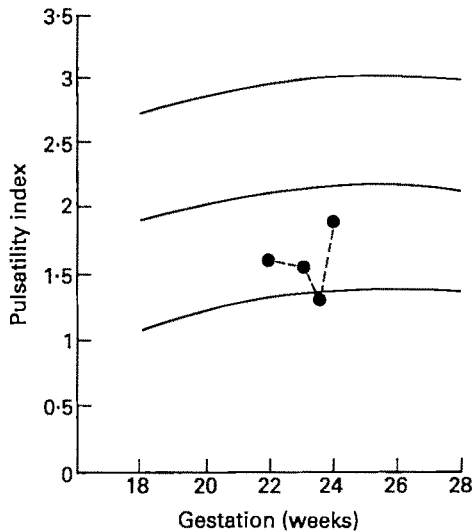


Fig. 1. Middle cerebral artery pulsatility index plotted against the reference range established by Vyas *et al.* (1990a).

Comment

It has been shown that fetal head compression and the consequential increase in intracranial pressure is associated with an increase in the PI of FVWs from the middle cerebral artery (Vyas *et al.* 1990b). A similar mechanism has been postulated for the raised PI of FVWs from the internal carotid artery in fetuses suffering from prolonged severe oligohydramnios (van den Wijngaard *et al.* 1988).

In small-for-gestational age (SGA) fetuses, the PI of FVWs from the fetal middle cerebral artery is reduced in proportion to the degree of fetal hypoxaemia, presumed to be causing cerebral vasodilatation. But it has been hypothesized that in severe hypoxaemia, the cerebral vaso-

dilatation is blunted by an increased intracranial pressure due to cerebral oedema (Vyas *et al.* 1990a). These conclusions were based on a cross-sectional study of 81 SGA fetuses.

In our patient, the FVWs were monitored in a serial fashion. The PI of the FVWs from the fetal middle cerebral artery initially showed a downward trend suggesting reduced cerebral vascular resistance. The last examination was performed 12 h before fetal death and this showed a sudden rise in the PI value. These observations are consistent with the hypothesis put forward by Vyas *et al.* (1990 *a & b*) and could represent an acute terminal pattern.

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SHORT COMMUNICATIONS

The endometrial status of women on long-term continuous combined hormone replacement therapy

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It is well established that progestogen therapy will completely abolish endometrial stimulation which results from oestrogen replacement (Thom *et al.* 1979). Cyclical addition of progestogens induces resumption of menses and other premenstrual-like symptoms which may lead to discontinuation of therapy. Continuous combined oestrogen/progesterone therapy overcomes these problems in most women (Staland 1981) but is not widely used. The concern seems to be that loss of the withdrawal bleed reduces endometrial protection. In addition there is no information on the long-term endometrial effects (Leather & Studd 1990).

This report presents our preliminary findings on the endometrial effects of prolonged use of a continuous combined regimen (2 mg oestradiol, 1 mg oestriol and 1 mg norethisterone daily, Kliogest, Novo) for hormone replacement therapy.

Subjects and methods

Fifteen women using Kliogest for hormone replacement therapy (HRT) were studied. The minimum duration of therapy was 3 years (58 women years of therapy, mean 3.9 years). All had an intact uterus and none had reported regular bleeding while on therapy. All had been reviewed at 6-months intervals since starting therapy.

Outpatient hysteroscopy was performed with

informed consent. Carbon dioxide was used to distend the uterine cavity. Endometrial sampling was performed in each woman using the Gynotest (Roussel), but no tissue was obtained. Hysteroscopically directed punch biopsies of endometrium and stroma were obtained from four women.

The biopsies were placed in tissue Tek OCT and orientated before freezing (Hawthorn *et al.* 1988). They were stored at -70°C . Frozen sections (4 μm thick) were cut later.

Oestrogen and progesterone receptors were stained using the avidin-biotin complex indirect immunoperoxidase method (Vector Laboratories) with diaminobenzidine as the chromogen. A rat monoclonal antibody to human oestrogen receptor (Abbot Laboratories-Erica Kit) and a mouse monoclonal antibody for progesterone receptor (Transbio-SARL) were used. Human non-genital skin was the negative control tissue and negative antibody controls comprised non-immune rat serum and irrelevant mouse monoclonal antibodies.

Results

In all women hysteroscopy, using intracervical Citanest, was well tolerated and the complete uterine cavity was inspected. No abnormalities were found, and in all the endometrium was thin and atrophic. Haematoxylin and eosin staining of frozen sections taken from the punch biopsies confirmed atrophic features.

Weak oestrogen receptor staining was observed in the nuclei of epithelial cells in two specimens. Strong progesterone receptor staining was seen in the nuclei of epithelial and stromal cells in three specimens.

Discussion

The addition of a progestogen to HRT may negate some of the advantages of replacing only oestrogen. There is concern about the possible adverse effects of progestogens on the lipid profile (Farish *et al.* 1983). Cyclical oestrogen/progesterone therapy tends not to improve the lipid

profile significantly, although decreased levels of low density lipoproteins occur on long-term treatment (Fletcher *et al.* 1984). Continuous combined regimens produce similar effects. The significance of increased apoprotein B remains to be determined (Farish *et al.* 1989).

It is surprising that continuous combined regimens have not become more popular since most women prefer to avoid the withdrawal bleed (Mitchell *et al.* 1990). Indeed there is little evidence to support its supposed benefit (Padwick *et al.* 1986). The finding of oestrogen and progestogen receptors in the nuclei of endometrial cells after long-term continuous oestrogen/progestogen replacement is very reassuring since it indicates that the progestogen is not abolishing the receptors induced by the oestrogen component.

The added progestogen is known to inhibit cell mitosis in the endometrium in the short-term (Magos *et al.* 1985). Our finding of atrophic endometrium on hysteroscopic examination, and confirmed histologically, provides reassurance that endometrial cell mitosis is inhibited in long-term use.

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Human immunodeficiency virus type 1 (HIV-1) seroconversion during pregnancy does not increase the risk of perinatal transmission

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Perinatal transmission of human immunodeficiency virus type 1 (HIV-1) infection is known to occur, but whether or not the transmission rate is influenced by the type of maternal infection is as yet unknown. We have followed, from birth, ten

children born to at risk mothers who had seroconverted to HIV-1 during pregnancy.

Subjects and methods

The risk factors associated with the mothers are reported in detail in Table 1. In particular, one woman (no. 1) claimed, after in-depth inquiry, that she had ceased intravenous drug use 3 years before the pregnancy and in that period she had had sexual intercourse only with her husband, who is seronegative. Another woman (no. 2) who had an infected partner reported that condoms had been used during intercourse from the beginning of pregnancy. All women had normal, full-term pregnancies (mean gestational age at delivery 39.8 weeks, range 39–41) and all of them were symptom-free at vaginal delivery. The mean birthweight was 3112 g (range 2550–3600 g), three babies were breast-fed (nos. 1, 3, 9), and the other seven were bottle-fed. Seven women knew they were at risk and had serological screening tests to assess their infection status either before or at the start of the pregnancy. As a result, most had one or more negative test result in addition to those reported in Table 1.

Specific HIV-1 antibodies were detected by enzyme-linked immunosorbent assay (ELISA; Abbott, Organon). Positive tests were confirmed by Western blotting. Serum p24 antigen was assessed by the standard method (ELISA, Abbott). Viral antigen expression in the child's peripheral blood mononuclear cells was assessed by indirect immunofluorescence using anti-p24, anti-gp41 and anti-gp120 monoclonal antibodies (Du Pont) (Tovo *et al.* 1987), while proviral DNA sequences were assayed by polymerase chain reaction.

Results

Table 1 indicates the gestational age at the last negative and first positive ELISA test. Western blot analysis of positive samples showed a diffuse pattern of antibody response in all but two mother-child pairs, with only anti-p24 antibody being present at delivery in one pair (no. 10) and anti-p24, anti-gp120 and anti-gp160 in the other (no. 8). As reported in Table 1, serum p24 antigen was absent at delivery in all seven women in whom it was assayed.

Two out of 10 children acquired infection and

Table 1. Characteristics of 10 at risk women who seroconverted to HIV-1 during pregnancy

No.	Associated risk factors	Gestational age (months)		Maternal AG at delivery	Child's age (months and infection status)
		At last negative test	At first positive test		
1.	i.v. drug use*	5	Term	–ve	30; uninfected (Ab–, AG–, PCR–, Ag Lct–)
2.	HIV+ partner	6	Term	nd	21; uninfected (Ab–, AG–, PCR–, Ag Lct–)
3.	HIV+ partner	5	Term	–ve	24; uninfected (Ab–, AG–, PCR–)
4.	i.v. drug use*	3	8	–ve	11; uninfected (Ab–, AG–, PCR–)
5.	HIV+ partner	2	6	–ve	18; uninfected (Ab–, AG–, PCR–)
6.	HIV+ partner	5	Term	nd	22; uninfected (Ab–, AG–, PCR–)
7.	i.v. drug use	1	Term	–ve	19; uninfected (Ab–, AG–, Ag Lct–)
8.	HIV+ partner	8	Term	–ve	7; uninfected (Ab–, AG–, Ag Lct–)
9.	HIV+ partner	5	Term	nd	22; infected (Ab+, AG+, PCR+)
10.	HIV+ partner	1	4	–ve	13; infected (Ab+, AG+, Ag Lct+, PCR+)

*Intravenous drug use stopped 3 years (no. 1) and 1 year (no. 4) before pregnancy.

Abbreviations: AG = serum p24 antigen; Ab = serum HIV antibodies; PCR = polymerase chain reaction for HIV-DNA, Ag Lct = HIV antigen expression in peripheral lymphocytes, nd = not done; –ve = negative.

developed some of the HIV-1-associated non-specific features that are included in the P-2A subclass of the CDC criteria (Centers for Disease Control 1987), at 11 months (no. 9) and at 9 months of age (no. 10). The other eight children were healthy, became negative for HIV-1 antibody, showed no viral markers and thus were considered as uninfected. The infant (no. 8) whose mother seroconverted in the last month of pregnancy seroreverted at 4 months, the others seroreverted at between 7 and 15 months of age.

Discussion

All women in our study seroconverted to HIV-1 during pregnancy. Their initial seronegativity was assessed only by ELISA test. Such a test does not detect all antibodies against HIV-1, but its negativity is commonly accepted as proof of lack of specific antibodies. That seroconversion actually took place during the pregnancy is further supported by the fact that most women had at least two sequential negative tests.

Two out of ten children acquired infection. This finding overlaps with the results from a large Italian Multicentre Study (1988) indicating that in our country 19% of children exposed perinatally acquire infection and seroconvert to HIV-1. Taken together these data strongly suggest that the risk of vertical HIV-1 transmission during primary infection is comparable to, or at least not higher than, that observed in chronic infection. Consequently, doubts arise on the importance of the immune response, in particular of some maternal antibodies (Rossi *et al.* 1989), in preventing mother-to-child virus transmission.

Antibody production to HIV-1 usually takes place within few months of infection. Based on this, the repeated lack of specific antibodies in patient no. 1, who claimed to have stopped intravenous drug use 3 years before pregnancy, was interpreted as proof of non-infection. In another woman (no. 2), her claim to be practising pro-

tected sexual intercourse during the pregnancy and her persisting seronegativity supported the decision to continue the pregnancy. There must be doubts about the reliability of these accounts, but a long-lasting silent infection cannot be ruled out when counselling high-risk seronegative pregnant women. In fact, an absent or delayed HIV-1 antibody response does not seem an exceptional event (Imagawa *et al.* 1989). In view of this, as a small number of women with high risk behaviour do seroconvert during pregnancy, it seems possible that the pregnancy itself may somehow trigger the HIV-1 immune response in previously unresponsive carriers.

Acknowledgment

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CORRESPONDENCE

Anti-Kell in pregnancy

Dear Sir,

We read with interest the recent paper detailing the Newcastle series of women with anti-Kell antibodies by Leggat *et al.*, [*Br J Obstet Gynaecol* (1991) 98, 162-165], but found this at almost total variance with our experience. As stated in the paper, Kell is an uncommon antibody, only 10-15% of the population being Kell positive with most women developing antibodies following a blood transfusion. Thus only 10-15% of women with antibodies will have a partner who is Kell positive and as most of these will be heterozygous, only approximately 50% will have a Kell positive fetus. Stated another way, for every 100 women with anti-Kell antibodies only a maximum seven will be in a position to have even a mildly affected fetus. The prognosis for this 7% will, however, be vastly different to the other 93%. Although this paper discusses the value of knowing the genotype of the partner, neither this nor the antenatal/postnatal genotype of the fetus is mentioned in the results. Both of these are critical to the correct management of the condition, and without them the contents of Table 1 are almost meaningless as statistically only around 14/194 will have a Kell positive fetus. It should thus come as no surprise that four women with titres of 1/2048 would have unaffected fetuses. Neither are any intrauterine treatments or the gestation at delivery mentioned.

During 1990 we were involved in the management of 10 women with anti-Kell antibodies, four of these had a Kell positive fetus and none of them had had a previous affected pregnancy. All these women had titres reported as high or very high. One other woman underwent a cordocentesis and was found to have a Kell negative fetus.

Two of the women were inappropriately managed by the referring general practitioner or consultant who failed to appreciate the importance of the condition and the rate at which deterioration can occur.

Both of these women had polyhydramnios and the fetuses had marked ascites together with scalp oedema in one. We have previously managed

another similar woman whose fetus had ascites and a pericardial effusion. This contrasts with no such fetuses over 25 years in Newcastle. All three fetuses became hydropic before 30 weeks gestation and in all of them the amniotic fluid Δ OD values were totally misleading being within the Liley midzone, i.e., false negatives as reported previously (Caine & Mueller-Heubach 1986). We find it difficult to explain the apparent occurrence of serious false positives described from Newcastle, and indeed no explanation is forthcoming in their discussion.

Of our four affected fetuses, one had four intrauterine transfusions and was safely born at 35 weeks, and another had one transfusion and was born 3 weeks later following an abruption. The lowest haematocrit in these two fetuses was 18 and 21% respectively. The third fetus was the most severely affected and was immediately delivered, and the baby survived. The outcome in the fourth affected fetus illustrates the unpredictability of the condition. The mother had a high level of anti-Kell antibodies with a positive partner. Cordocentesis showed the fetus to be Kell positive but with a negative direct Coombs test. No treatment was required antenatally, the results were confirmed after birth, but the baby required phototherapy.

We would agree that anti-Kell antibodies are extremely unpredictable and cannot be assessed using the same methods as described for anti-D such as amniocentesis and optical density measurements, but we cannot agree that the condition with a Kell positive fetus is as benign as the paper implies and a thorough understanding of the importance of this condition and its unpredictability is vital to all who deal with pregnant women.

A simple protocol should be followed in all such pregnancies (i) Check the Kell status of the partner. If negative treat as a normal pregnancy and ignore antibodies. (ii) If partner is Kell positive refer for cordocentesis after 20 weeks. If the fetus is negative treat as a normal pregnancy and ignore antibodies. (iii) If the fetus is Kell positive refer for management and treatment at a centre dealing with this problem regularly, where cordo-

centesis and intrauterine intravascular transfusion can be employed.

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British Journal of Obstetrics and Gynaecology
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Anti-Kell in Pregnancy

Dear Sir,

Leggat *et al.* [*Br J Obstet Gynaecol* (1991) 98, 162-165] concluded that 'haemolytic disease caused by anti-Kell is less severe than suggested by some workers'. The reports to which they refer for comparison are small and we recognize that they will have bias. However, we feel that Leggat *et al.* give false reassurance to clinicians confronted with the problem of Kell alloimmunization as a cause of haemolytic disease of the newborn. Their series is based on 194 pregnancies with documented anti-Kell antibodies which resulted in 16 affected fetuses, none of which died, and none of which was hydropic, despite three having severe anaemia.

The authors note that the majority of women with anti-Kell antibodies have Kell negative partners and were sensitized by a previous blood transfusion rather than by pregnancy. However, they fail to include the partner's Kell genotype in their data. Thus, one can only guess the relevance of the 'unaffected' row in Table 1. Of the babies with Kell positive fathers, which were therefore at risk from haemolytic disease, how many were Kell positive but unaffected? We note that the 16 affected pregnancies occurred in 12 women, but no further details are given regarding these affected families. Whether the three severely affected pregnancies were first or subsequent pregnancies and what the gestational ages were at delivery were not stated, despite the fact that this may dramatically affect outcome.

As a referral centre for intrauterine intravascular transfusion, our institution has treated seven Kell positive fetuses with haemoglobins

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below 7.5 g/dl since 1986. All but one woman presented before 26 weeks gestation, including two at 19 weeks. Two fetuses were hydropic and one had early ultrasound evidence of ascites. Of the seven women, two had had previous intrauterine deaths, whilst four had no previous history of affected babies. For one of the women the first infant required phototherapy at term, the second was a severely affected fetus hydropic at 27 weeks, prior to her third affected pregnancy which required intrauterine intravascular transfusions from 25 weeks gestation.

There is a spectrum of severity, which is largely predicted by obstetric history, but unlike D alloimmunization, we have found that the severity at the initial presentation of anti Kell induced haemolytic anaemia is unpredictable.

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Author's reply

Dear Sir,

We are grateful to Constantine *et al.* and to Vaughan *et al.* for their interest in our paper and feel there is much common ground. We and they believe that there are important differences between this disease and that caused by anti-D. The calculations by Constantine *et al.* in their first paragraph reflect closely what we actually found. We did not suggest that this is a benign disease. By 'less severe' we mean that we doubt whether the

loss rate due to anti-Kell is as great as 57% (16 of 28 pregnancies in the three series described). We stated in our discussion that a significant stillbirth rate could have been missed and, as luck would have it, since our paper was written we have had two severely affected babies requiring intra-uterine transfusion, one of whom died 28 days after birth. Failure to observe a stillbirth or hydropic fetus in 16 affected pregnancies will not exclude with 95% confidence potential stillbirth or hydrops rates below 20%. Three of our affected infants were 'very severe'. Although we have seen infants severely affected by multiple antibodies, one of which was anti-Kell, our study excluded all patients in whom antibodies other than anti-Kell were present.

We assumed that all the infants with a positive direct Coombs test were Kell positive because anti-Kell was the only antibody detected in their mothers. One or two of the apparently unaffected infants might conceivably have been Kell positive but with only very small amounts of antibody on their red cells. This could only have improved the overall outlook for Kell positive infants in our study group. No fetus received intrauterine transfusion in our study group.

Although we made no statistical point about Table 1, it is far from meaningless. It shows that, if the fetal Kell group is unknown (as is the case whenever the father is heterozygous), it is impossible from the antibody titres to predict an affected fetus because the range associated with *unaffected* fetuses (presumed Kell negative) overlaps entirely that associated with affected fetuses.

It is unnecessary to 'explain' occasional false positive results of amniotic fluid examination unless one were to start testing with the presumption that they could not occur. The simple conclusion is that the test is not good enough to predict which pregnancy associated with anti-Kell is likely to benefit from intervention.

It is difficult to comment on the anecdotes offered by either group except to say that we sympathise with them and, again, do not deny the observed severity of individual cases. Our study was too small to draw useful conclusions about the severity of disease in successive pregnancies and, because there were no fetal or neonatal deaths, we can not comment on the impact of gestation on survival.

Finally, the plan of management suggested by Constantine *et al.* has appeal and a case for cordocentesis, which we mentioned in our paper, can be made. We assume that neither group disagrees strongly with our view that reduction of transfusion induced sensitization would be of value. Our study provides impetus for the development of alternative management strategies but was not intended to devise them.

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British Journal of Obstetrics and Gynaecology
September 1991, Vol. 98, pp. 945-946

Obstetric accidents: the patient's perspective

Dear Sir,

The April edition of the Journal carried an excellent and telling article on obstetric accidents by Vincent *et al.* [*Br J Obstet Gynecol* (1991) **98**, 390-395]. Indeed, the recommendations and suggestions of this article could, I feel, be applied even more widely to gynaecological and other surgical practices.

A feature of the article was the criticism of standards of care arising from the absence of senior staff. In almost 20% of cases, a doctor was called

but arrived late or did not arrive. In many units, senior staff may be committed elsewhere and their response to a request for help from the delivery suite may not be as rapid as might be preferred. This can be a particular problem if staff are based at more than one site.

It may not be possible to define what were the delaying factors but unless the person who was late or did not arrive makes a note in the relevant records to explain why they were so delayed, their silence will later be interpreted to imply a failure to deliver proper standards of care. Perhaps this

should be a recommendation in the event of such a not infrequent occurrence.

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British Journal of Obstetrics and Gynaecology
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The crown-rump length in early human pregnancy: a reappraisal

Dear Sir,

I read with interest the paper by Schats *et al.* [*Br J Obstet Gynaecol* (1991) **98**, 460-462]. I note that of the 59 embryos studied, 33 were from multiple pregnancies. Original reference curves for crown rump length (CRL) measurements were derived from data collected on singleton pregnancies (Robinson 1973; Robinson & Fleming 1975). It could be argued that some of the discrepancies observed by Schats *et al.* between their data and earlier reference curves are due to differences in early growth patterns between multiple and singleton pregnancies. They are uncertain whether results from in-vitro fertilization (IVF) pregnancies can be extrapolated to naturally conceived pregnancies.

I am currently studying early pregnancy changes in 51 women with defined dates of conception. Thirty four have conceived following IVF, the remainder are pregnant following timed intercourse in a monitored natural cycle or following donor insemination. Forty of the pregnancies are singleton, eight are twin and three are triplet. My data show no differences in first trimester growth patterns between singleton and multiple pregnancies. They also show no differences in CRL measurements between IVF pregnancies and those conceived naturally, a finding

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supported by others (Evans 1991; MacGregor *et al.* 1987).

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September 1991, Vol. 98, pp 946-947

First trimester CA 125 and Down's syndrome

Dear Sir,

The short communication by van Lith *et al.* [*Br J Obstet Gynaecol* (1991) **98**, 493-494] is

interesting in that, similarly to a communication from this department (Spencer, 1991a), it sets out to examine further the observations of Check *et al.* (1990) who reported three women with ele-

Table 1. Distribution statistics for maternal serum CA 125 in pregnancies affected by Down's syndrome and unaffected pregnancies

	Serum CA 125 (MoM)	
	Down's pregnancies (n = 25)	Unaffected pregnancies (n = 125)
5th centile	0.40	0.40
Median	0.945	1.02
95th centile	2.00	2.00
Log mean (SD)	-0.03 (0.21)	0.01 (0.20)
Transformed range $\pm 2SD$	2.40-0.36	2.58-0.41

MoM = multiples of the median.

vated early first trimester serum CA 125 concentrations, who then miscarried in the late first trimester or early second trimester, the three fetuses were chromosomally abnormal (Trisomy 12 & 13, 45X, Trisomy 21).

Unlike the van Lith study I investigated maternal serum CA 125 levels in 25 second trimester pregnancies affected by Down's syndrome each one matched with five unaffected control pregnancies for gestational age (± 3 days), maternal age (± 6 months) and duration of sample storage (± 1 month). Table 1 shows the population distribution (after log transformation of the data) for the unaffected and Down's pregnancies. Maternal serum CA 125 concentrations of the Down's pregnancies in the second trimester showed no statistically significant difference from those in the unaffected group—unlike the lower values observed by van Lith in the first trimester. Clearly the difference between our two studies suggests either that maternal serum CA 125 responds differently in the first trimester, similar to that seen with pregnancy specific β -1 glycoprotein (SP1) which has a better predictive value in the first trimester (Brock *et al.* 1990) than in the second trimester (Wald *et al.* 1989; Spencer 1991b), or that storage of samples at 20°C or the small number of samples in the van Lith *et al.* study has introduced a bias.

The unsubstantiated conclusion that the high levels reported by Check *et al.* (1990) may have been a result of threatened miscarriage has been substantiated in my study (Spencer 1991a). In 10 pregnancies complicated by intrauterine death and in 10 pregnancies ending in miscarriage (with no genetic abnormalities), maternal serum CA 125 concentrations were greater than 2 MoM in 40%, with a median MoM of 1.90. Thus the elevated maternal serum CA 125 levels in the three

pregnancies described by Check *et al.* (1990) are most likely to relate to impending fetal death.

I feel that the evidence points to maternal serum CA 125 not being a second trimester marker of Down's syndrome and that the case for its role as a first trimester marker needs further clarification and study. I await further retrospective and prospective studies in the first trimester with interest.

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British Journal of Obstetrics and Gynaecology
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Idiopathic thrombocytopenic purpura in pregnancy; A randomized trial on the effect of antenatal low dose corticosteroids on neonatal platelet count

Dear Sir,

I read with interest the letter from L. J. Roberts [*Br J Obstet Gynaecol* (1991) **98**, 334-335] following the publication of the article by Christiaens *et al.* (1990). Dr Roberts' concern regarding a fall in the platelet count in the neonatal period is justified though this is not due to anti-platelet IgG from breast milk since there is little evidence that absorption of IgG in human milk occurs (Lucas 1986).

The worsening thrombocytopenia is more likely due to the development of the neonatal splenic circulation and the more efficient removal of antibody coated platelets (Letzky 1989). I would agree with the reply of Christiaens *et al.* (1991) that breast-feeding need not be discouraged in women with idiopathic thrombocytopenic purpura.

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British Journal of Obstetrics and Gynaecology
September 1991, Vol. 98, p. 948

Patient selection for hysteroscopic endometrial resection

Dear Sir,

In their article Rutherford *et al.* [*Br J Obstet Gynaecol* (1991) **98**, 228-230] suggest that there could be considerable financial benefits to the NHS if minimally invasive methods are used in place of hysterectomy for women with menorrhagia. However, this prediction is based on a retrospective study looking at women who have already undergone hysterectomy.

Our unit, at St Mary's Hospital in Manchester, is performing radiofrequency endometrial ablation (RaFEA) and we are being referred a considerable number of women who would be considered unfit for hysterectomy (or who would refuse hysterectomy). Currently more than 40% of our referrals fall into this category.

If these techniques become firmly established, such women will form a new subgroup of patients seeking operative treatment. Such minimally invasive procedures as endometrial resection or RaFEA should be considered not only as alternatives to hysterectomy but also as alternatives to medical management. Any financial considerations must take such factors into account.

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BOOK REVIEWS

Nutrition and Metabolism in Pregnancy: Mother and Fetus, by Pedro Rosso, Oxford University Press, Oxford 1991. 324 pages, with figures and tables, £45.00

The importance of nutrition in pregnancy has largely been undervalued. Most publications on the subject concentrate on one particular aspect or another. So it was a refreshing change to read this comprehensive review.

This is an excellent reference source on virtually all facets of Nutrition and Metabolism in Pregnancy—in other words a book that actually lives up to its title! There are nine chapters in total ranging from maternal metabolism in pregnancy to fetal growth, from maternal-fetal nutrient exchange to fetal consequences of vitamin and mineral deficiency. Each chapter is written in a well balanced style and is very well referenced. The various problems inherent in research on the subject of nutrition in pregnancy are constantly stressed. I was particularly impressed by the sections on nutritional care in normal pregnancy and in pregnant women with special problems (such as poor calorie intake, obesity, diabetes, food aversions and cravings and mothers with 'alternative' dietary practices). These will be especially useful as a reference source when confronted by professional colleagues or mothers asking 'what is a sensible diet in pregnancy?' or 'what are the dangers of a particular diet?'

In summary, I liked the book and would recommend it as a useful reference source. At £45 it is probably more appropriate for libraries than individuals.

David James

Miscarriage: Women's Experiences and Needs, edited by Christine Moulder, Pandora Press, London, 1990. 254 pages, £5.99.

Christine Moulder is a social worker and mother, has experienced miscarriage herself and is active in the Miscarriage Association. This book

focuses very much—as its sub-title indicates—on the experiences of women having miscarriages, and on the needs they express and the implications of these for health professionals providing care. The questions from women which make up the central text of the book come from 320 who filled in a Miscarriage Association questionnaire and 30 interviewed in depth by the author.

The value of this book lies in the embedding of miscarriage as a medical, social and personal experience in the words of women who have been through it. Though there are references to medical evidence about the causes and treatments of miscarriage, these are not comprehensively explored or referenced. The messages of the book are not original, but according to the data provided by the women, still need to be drawn to the attention of health professionals: miscarriage is often (though by no means always) an event which shocks, hurts and disturbs deeply held notions about 'proper' womanhood; there may be long-term implications for women's mental and physical health and for family relationships. The role of health professionals is therefore crucial. The book contains a section on 'Guidelines for Good Practice' which should be mandatory reading (It struck me that most of the guidelines would do as well for the rest of maternity care). But in particular, perhaps, doctors, midwives and nurses need to be aware of the need to avoid offensive language (as in one doctor's offer to 'hoover you out' as a euphemism for a D & C), of the importance of giving information (and acknowledging when there is no information to give); and in understanding that although, in their eyes, miscarriage is a medical event, to women and their families it has another set of meanings altogether.

Ann Oakley

Birth Defects Encyclopedia edited by Mary Louise Buyse. Centre for Birth Defects Information Services, Dover, USA 1990. 1892 pages with figures and tables, £150.

This comprehensive volume of 1892 pages has

contributions from over 1000 authors and an editorial panel in excess of 60 members. As is to be expected with such a wide authorship the quality of the entries varies but the majority are up to date and accurate. Information on each condition is listed under headings covering clinical, epidemiological and genetic aspects together with relevant references. Each entry is cross-referenced to 'Mendelian Inheritance in Man', to a dysmorphology database and to other entries, providing check lists for differential diagnosis. Unfortunately the headings take up more type-space than the actual information in some entries. I particularly enjoyed the sections entitled 'special considerations' as they contained interesting historical data and information from the literature.

The encyclopedia is amply illustrated by black and white figures which, although not all of good quality, show different features of the disorder in question in a composite frame and are useful additions. They do, however, pick out the extreme phenotypes and are not ideal to show to patients.

Although this book aims to cover all birth defects known to man, and it is certainly difficult to name a condition not mentioned therein, readers are well-advised to make use of the listed references to read about subjects more widely. I would envisage this book to be of use on a general paediatric ward or ante-natal clinic for 'on the spot' information prior to referral of the patient to the relevant specialist.

Most of the contributors to this book are from the US and Canada and this is reflected in the general reading of the text. It is produced by a non-profit-making organization but is expensive at £150 and thus it would be wise to also consider alternative catalogues when making a choice of reference book for a department.

Jill Clayton-Smith

Human Prenatal Diagnosis. Second edition revised and expanded, edited by Karen Filkins & Joseph F. Russo, Marcel Dekker Inc., New York, 1990. 624 pages, \$150 (US and Canada), \$180 all other countries.

Pre-natal diagnosis is one of the rapidly expanding growth areas in obstetric practice. As a subspecialty, it is now virtually unrecognizable compared with the situation that existed ten years ago. This book, which is a revised and expanded

second edition, concentrates on the procedural and mechanical approaches to diagnosis, according to the foreword written by one of the contributors. It is, however, a book aimed predominantly at a North American audience and this is most obvious in the introductory chapter overviewing the principles of antenatal and neonatal screening and in the penultimate chapter which addresses the legal aspects surrounding diagnostic and therapeutic procedures during the antenatal period.

The literary style and content vary considerably with the chapters. The chapter on chorion villus sampling describes the experience, which is considerable, from one centre, with relatively little reference to that published from other units with similar large experiences. It concentrates predominantly upon the transcervical method of sampling and pays little attention to the transabdominal route which appears to be gaining popularity around the world. Unfortunately there is virtually no mention of chorion villus sampling performed during the second and third trimester, which should be described, since there is a place for this procedure in obstetric/genetic practice. By contrast, the chapter on amniocentesis gives a good overview of the procedure, referring to the literature to provide a balanced opinion of the associated risks and benefits. Unfortunately there is no mention of the value of measuring acetylcholinesterase in amniotic fluid for the detection of open neural tube defects.

There are three chapters concerned with ultrasound. One concentrates on first trimester examination and gives a rounded description of the rôle of sonography at this stage of pregnancy, and is appropriately guarded about its reliability at this stage. There is a chapter devoted to second trimester ultrasound which adopts a somewhat philosophical approach and generally deals with the subject very superficially. The chapter devoted to the third trimester in some part duplicates that involving the mid-trimester. In addition there are a large number of ultrasound pictures, many of which do not assist the reader in understanding or appreciating the subject. The division between second and third trimester would appear to be somewhat artificial and the text would probably benefit from amalgamation of the two chapters.

The highlight of the book is the chapter devoted to applied molecular genetics and the detection of genetic disorders by DNA analysis. This constitutes approximately one-fifth of the

volume, is written with commendable clarity and, for me, made the review of this volume well worthwhile. Not only does it reinforce a basic understanding of molecular biology and its relation to prenatal diagnosis, but the application to specific disorders and system diseases is discussed in detail.

Among the other chapters, that concerned with prenatal diagnosis in cases of multiple pregnancy and the dilemmas involved in selective fetocide provides a good objective overview of published work and would be helpful to the practising obstetrician/geneticist when confronted by this situation, while the chapters concerned with serum afp screening and sampling fetal blood are both dealt with somewhat superficially and concentrate on the experiences of the authors rather than the published literature. The chapter devoted to fetal therapy similarly concentrates on the experiences of the authors at the expense of the experiences reported from various centres around the world. Fetal echocardiography and blood flow investigations is well reviewed; the ultimate value of the latter is rightfully left uncertain at the present time, although the need to assess objectively the value of Doppler blood flow studies before introduction into routine screening practice has not been adequately stated. The black and white reproduction of a colour flow image demonstrating a patent foramen ovale at 15 weeks' gestation on page 64 would appear to leave something to the imagination!

The most cogent reason for buying this volume is to attain a greater understanding of the science of molecular genetics and its application to prenatal diagnosis. Many of the chapters are well referenced, although there is a predominance of citations to work originating from North America, often at the exclusion of the original publications from elsewhere in the world. There are a number of typographical errors, including the inconsistent listing of bibliography at the end of chapter 4, compared with the other chapters; this would not be expected in a second edition.

With such a rapidly evolving subject the editors are to be commended for producing a volume which is so up to date. It will, however, require a third edition within the next few years, and, with the reservations expressed about some of the chapters, \$180 could be better used in purchasing other texts on this subject.

I. Z. Mackenzie

Medical Negligence Case Law by Rodney Nelson-

Jones & Frank Burton. Fourmat Publicity, London 1990. 408 pages, £39.50

This book is a first rate and comprehensive introduction to the concept of Medical Negligence. It is divided into two parts. The first is smaller and contains accounts of the whole concept of medical care. Initially courses of action are described; battery, negligence, vicarious liability and liability in contract. Next comes medical malpractice, including the concept of care and standards of skill and care. Following that common types of action are described, with specific sections on failure to diagnose, consent, surgical mishaps and obstetric mishaps. The first part concludes with a discussion on damages and a description of the process of litigation. The whole of this part is liberally illustrated with case law; if you do not know how *McDermid v Nash Dredging and Reclamation Company Limited* is relevant to obstetrics you can find out on page 13.

The second half contains case reports—nearly 300 of them. These have been chosen to illustrate various legal concepts, and how judges at various levels have applied the law. These include such essentials as *Bolam* and *Siddaway*, and many more besides. All are of value, and merit study.

This is a book by lawyers for lawyers; it is one of a series of law books. Its style is terse, and unfamiliar legal terms and phrases abound. For doctors it is a hard read. Nevertheless I cannot recommend it too highly. It puts into words what we so often allow to become blurred, our legal and proper relationship with our patients. If the next generation of doctors can understand this better perhaps today's burning issue, the fear of litigation, will become less prominent.

John Hare

Books received some of which may be reviewed at a later date

The Surfactant System of the Lung. Prevention and Treatment of Neonatal and Adult Respiratory Distress Syndrome edited by E. V. Cosmi, G. C. Di Renzo & M. M. Anceschi. Macmillan Press, Basingstoke and London, 1991, 216 pages with figures and tables, £45.00

Progress in Obstetrics and Gynaecology Volume 9 edited by John Studd. Churchill Livingstone, Edinburgh, London, 1991, 420 pages, illustrated, £24.95

Atlas of Breast Disease by V. Barth & K. Prechtel.

B. C. Decker Inc., Philadelphia, 1991, 262 pages fully illustrated, £88

Homebirth and Other Alternatives to Hospital by Sheila Kitzinger. Photography by Marcia May. Dorling Kindersley, London, New York, Stuttgart, 1991, 208 pages, fully illustrated with photographic plates, £12.99

100 Case Histories in Obstetrics & Gynaecology edited by Michael D. G. Gillmer, Phillip J. Steer & Julian Woolfson. Churchill Livingstone, Edinburgh, London, 1991, 295 pages, £10.95

The BBC Pregnancy and Post-natal Exercise Video with Rosemary Conley & Jane Ashton. BBC Video 90 minutes duration. Available from video stockists, £10.95

Current Clinical Topics in Infectious Diseases edited by Jack S. Remington & Morton N. Swartz. Blackwell Scientific Publications, Boston,

Oxford, London, 1991, 294 pages with figures and tables, £49.50

Proceedings and Symposia

Antenatal Diagnosis of Fetal Abnormalities (Results of a Study Group held by the Royal College of Obstetricians and Gynaecologists) edited by J. O. Drife & D. Donnai. Springer-Verlag, London, Berlin, 1991, 363 pages with figures and tables, £65

The Diffusion of Four Prenatal Screening Tests Across Europe (A Study of the Diffusion of Medical Technology in Europe) by Margaret Reid. Published by The King's Fund Centre 1991, 133 pages with figures and tables £9.95. Available from the King's Fund Centre for Health Services Development, 126 Albert Street, London NW1 7NF or by post from Bailey Distribution Ltd, Dept. KFP, Learoyd Road, Mountfield Industrial Estate, New Romney, Kent TN28 8XU

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British Journal of Obstetrics and Gynaecology

Vol 98 No 9 September 1991

CONTENTS

- 847 Commentaries
Stopping smoking—again
J. Lumley
First trimester prenatal diagnosis: chorion villus sampling or amniocentesis?
J. P. Neilson & C. M. Gosden
- 853 Some historical aspects of toxæmia of pregnancy. A review
I. Loudon
- 859 Cotinine-assisted intervention in pregnancy to reduce smoking and low birthweight delivery
J. E. Haddow, G. J. Knight, E. M. Kloza, G. E. Palomaki & N. J. Wald
- 866 Early amniocentesis: alphafetoprotein levels in amniotic fluid, extraembryonic coelomic fluid and maternal serum between 8 and 13 weeks
N. C. Wathen, P. L. Cass, D. J. Campbell, M. J. Kitau & T. Chard
- 871 Doppler investigation of uteroplacental blood flow resistance in the second trimester: a screening study for pre-eclampsia and intrauterine growth retardation
S. Bewley, D. Cooper & S. Campbell
- 880 Thyrotrophin-releasing hormone—a lactation-promoting agent?
F. Peters, J. Schulze-Tollert & W. Schuth
- 886 The effect of maternal anaemia and iron deficiency on the ratio of fetal weight to placental weight
K. M. Godfrey, C. W. G. Redman, D. J. P. Barker & C. Osmond
- 892 Fetal blood sampling and pregnancy loss in relation to indication
D. J. Maxwell, P. Johnson, P. Hurley, K. Neales, L. Allan & P. Knott
- 898 Mode of delivery and neonatal death in 17 587 infants presenting by the breech
J. L. Kiely
- 905 Maternal serum unconjugated oestriol and human chorionic gonadotrophin levels in twin pregnancies: implications for screening for Down's syndrome
N. Wald, H. Cuckle, T. Wu & L. George
- 909 Haemorrhagic problems in obstetrics and gynaecology in patients with congenital coagulopathies
I. A. Greer, G. D. O. Lowe, J. J. Walker & C. D. Forbes
- 919 Magnesium intake and status and pregnancy outcome in a Danish population
K. Skajaa, I. Dørup & B.-M. Sandström
- 929 Immunocytochemical localization of neutrophil elastase in term placenta decidua and myometrium in pregnancy-induced hypertension
B. H. Butterworth, I. A. Greer, W. A. Liston, N. G. Haddad & T. A. Johnston
- 934 Unfavourable pregnancy outcome associated with congenital protein C deficiency. Case reports
D. Bertault, L. Mandelbrot, C. Tchobrousky & Y. Sultian
- 937 Fetal middle cerebral artery flow velocity waveforms—a terminal pattern. Case report
R. Chandran, V. Serra Serra, S. M. Sellers & C. W. G. Redman
- 939 Short communications
The endometrial status of women on long-term continuous combined hormone replacement therapy
R. J. S. Hawthorn, K. Spowart, D. Walsh & D. McKay Hart
Human immunodeficiency virus type 1 (HIV-1) seroconversion during pregnancy does not increase the risk of perinatal transmission
P.-A. Tovo, E. Palomba, C. Gabiano, L. Galli & M. de Martino
- 943 Correspondence
- 949 Book reviews

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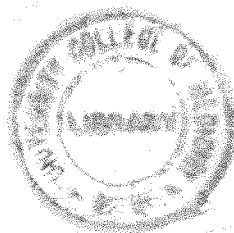
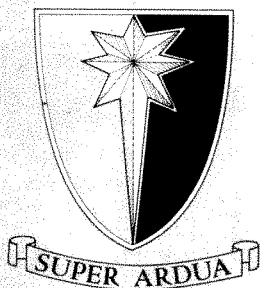
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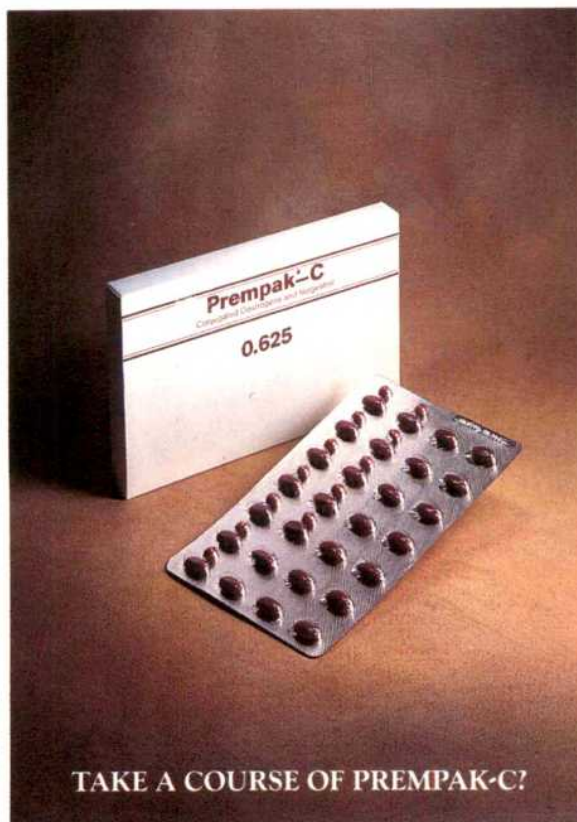
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Wyeth

COMMENTARIES

Health after childbirth

We have carried out an investigation, the first of its kind, into the nature and extent of long-term health problems beginning for the first time soon after childbirth. In particular we have searched for potential determinants of these health problems from among a wide range of social, obstetric and anaesthetic factors and the findings are to be published as a book by HMSO in November (MacArthur *et al.* 1991). Long-term morbidity after childbirth has been a neglected area of research. A few studies have followed up specific problems, such as perineal management and urinary incontinence (Sleep & Grant 1987) or depression (Kumar & Robson 1984; Watson *et al.* 1984), but there has been no comprehensive assessment of the extent of problems experienced by women.

This present study is based upon a sample of 11 701 women giving birth to their most recent child, in one hospital in Birmingham between 1978 and 1985. Information on health problems was obtained through a postal questionnaire sent in January 1987, and this was linked to the full maternity case-notes for each woman. The main investigation was limited to symptoms not previously experienced by the woman so that they could be related specifically to the circumstances of a particular delivery. Recurrent symptoms, including those starting during the pregnancy, were discarded. Complaints lasting 6 weeks or less were also excluded since our main concern was with longer-term health problems. Most of the symptoms reported by the women had lasted more than a year, and around two-thirds (varying slightly for specific symptoms) were still present at the time of the enquiry, 13 months to 9 years later. Investigation was also limited to symptoms first occurring within 3 months of the birth, although in fact the majority started within the first week.

The research stemmed from an initial concern of obstetric anaesthetists as to whether epidural anaesthesia had any long-term consequences.

However, the technical necessities of the research design, the opportunities of the situation and the lack of previous research in the area, led to a widened investigation of post-partum morbidity in general, including an examination of social and obstetric factors along with the anaesthetic ones.

The extent and the persistence of the reported morbidity surprised us: 47% of the women reported at least one new health problem, starting within 3 months of the delivery and lasting more than 6 weeks. The analysis of the social and obstetric associations of the symptoms was based on multivariate discriminant analysis and on multi-way tabulations. Potential determinants were those factors remaining as independently associated after taking account of inter-related factors using both forms of multivariate comparisons.

Backache was a common health problem after delivery, reported by 1634 women (14%). Many backaches had become chronic, with 65% still unresolved at the time of the enquiry. There was a powerful association with epidural anaesthesia: 18.9% of women reported backache after an epidural compared with 10.5% after non-epidural deliveries (MacArthur *et al.* 1990). This difference was consistently present in many different circumstances, and the excess of 'abnormal' deliveries occurring with epidural anaesthesia did not seem to account for the association; nor did varying pain tolerances.

Spinal anaesthesia, a long second stage labour and Asian ethnic group were additional independent predictors of backache. The only circumstance in which an epidural did not increase the risk of backache was after elective caesarean section. We have hypothesized that the backache-producing mechanism is postural, occurring generally during labour, but exacerbated by epidural anaesthesia, through loss of muscle tone, inability to move, and inhibition of discomfort-feedback. Additional events in the

post-partum environment (e.g., lifting, bending) sometimes seems to trigger the onsets.

Newly occurring frequent headaches were reported by 3.6% of the sample; and 71% of these lasted over a year. Migraine was reported by 1.4%, and 85% lasted over a year. The two symptoms combined together seemed to resolve into two separate headache 'syndromes'. One group occurred with backache, was closely associated with epidural anaesthesia, was more frequent among Asian women and often began immediately after delivery. The second group was unassociated with backache or epidurals, was more frequent in younger women and those with more than one child, and began any time within the first 3 months and sometimes later. We propose that the headaches in the first group are probably secondary symptoms of an epidural-related spinal-axis 'syndrome' of which backache is the main component. The second group more likely represents a response to social stresses within the post-delivery environment.

Additional musculo-skeletal symptoms (neckache; shoulderache; pain and weakness in the limbs and tingling in hands and feet) were individually infrequent, but overall were reported by 8.2% of the sample. Neckache and tingling in the hands/fingers appeared as additional components of the already proposed epidural-related spinal-axis 'syndrome'. A striking excess of musculo-skeletal symptoms occurred in Asian women, especially pains and weakness in the limbs, where there was a four-fold excess. These symptoms might result from latent osteomalacia, exacerbated by the metabolic and physical stresses of pregnancy and delivery. Finally, a small number of women reported various combinations of neckache, shoulderache and pain in the arms associated with caesarean section, especially under general anaesthesia. Positioning of the neck to facilitate intubation would provide a plausible explanation.

These various associations found for backache, headache and other musculo-skeletal symptoms general illustrate the extreme sensitivity of the skeletal/ligamentous system of parturient women.

Newly occurring stress incontinence, still unresolved, was reported by 10.6% of the women; this was so even after a first birth. It was associated with long second stage labours and large babies, and in some circumstances with forceps delivery. Increasing maternal age was also an important predictor. Caesarean sections

resulted in fewer symptoms but even here the age association remained. Other investigators of childbirth stress incontinence (Snooks *et al.* 1986; 1990) have proposed that much of this occurs through injury to the pudendal nerves. The obstetric factors associated with this type of injury corresponded in part, but not in full, with the symptom predictors in this present study.

Urinary frequency was less common, reported as still unresolved after 4.4% of births. Many cases occurred jointly with stress incontinence and the main predictors were similar. However, it occurred alone in 2% of the sample, and then had no major delivery or maternal associations. It is postulated that urinary frequency alone might have an infective rather than a traumatic component.

Haemorrhoids starting after delivery and still unresolved were reported by 5.3% of the women; 6.9% among primiparae. Reassurances in some obstetric textbooks (Iffy & Kamnietzky 1981) that childbirth-induced haemorrhoids disappear soon after the delivery are unfounded. Unlike stress incontinence, the risk of new symptoms declined with increasing parity, suggesting a selective prior susceptibility with symptoms precipitated by the first delivery. Long second stage, forceps and heavier babies all increased the risk of haemorrhoids; whereas Asian ethnic group and caesarean section were associated with fewer symptoms. Only 4.2% of the sample reported haemorrhoids after caesarean section, compared with 18% after a second stage of 3 h or more with a forceps delivery.

Depression was reported by 9.1% of the women and 12.2% reported extreme tiredness. Both were shorter-lasting than most of the other symptoms: 60% of the depressions and 50% of fatigues had resolved within a year. Depression and fatigue were both associated with a long first stage of labour; and depression with caesarean section, but only after a first birth. Post-partum haemorrhage was associated with fatigue probably through undiagnosed and/or inadequately treated anaemia. However, the main predictors of depression and fatigue were located within the domestic environment. Depression was more common among young mothers, and less common among Asians. Fatigue was more common among older mothers, especially after a first birth. The unmarried state was highly predictive of depression and of fatigue, especially together, and of long-lasting symptoms. Twins showed a similar relation, as did a small baby. Breast feed-

ing was also associated with short-term fatigue and depression.

In general, many women did not consult a doctor with their post-partum symptoms: only 31% of those with backache went to the doctor; 48% of those with depression/anxiety; 48% of those with frequent headaches; and 14% of those who had stress incontinence. The reason for non-consultation is not known, but might be related to perceptions of available treatment or to the severity of symptoms, about which we had no information. Whatever the reason, the effect is that the full extent of post-partum morbidity is not recognised by the medical profession.

The findings of this study fit within a general model aetiological framework comprising three related sets of potential symptom determinants. They are located in the background of the mother before the birth, the delivery itself and the post-partum environment. Each set offers implications for different types of further research, including preventive or therapeutic interventions conducted on a trial basis. Following a necessary confirmation of the findings, the investigators recommend that consideration be given to a re-defined mode of postnatal follow-up, providing a progressive schedule of discharge rather than routine discharge at 6 weeks. In particular this should contain specific provision for the recognition, treatment (where possible) and overall monitoring of the forms of medium and long-term morbidity identified in this study.

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December 1991, Vol 98, pp. 1195-1199

The Robertson-Brosens-Dixon hypothesis: evidence for the role of haemochorial placentation in pregnancy success

Development of the fetus and placenta is dependent upon an adequate maternal blood supply. It is now clear that a range of pregnancy disorders, such as pre-eclampsia, intrauterine fetal growth retardation, placenta accreta and miscarriage, may ensue when there is defective

haemochorial placentation. The unravelling of the complexities of materno-trophoblastic interaction owes much to the morphological studies of the human placental bed.

During early pregnancy, extravillous trophoblast derived from the cytotrophoblastic shell

and tips of anchoring villi infiltrate into the placental bed, viz., the decidua basalis and subjacent superficial myometrium. Interstitial trophoblast tend to cluster around spiral arteries while endovascular trophoblast migrate retrogradely into the lumina of the spiral arteries and invade the arterial wall. The muscular and elastic components of the arterial wall are replaced by fibrinoid thus transforming the small calibre vessels into flaccid distended tubes. These changes, termed physiological vascular changes (Brosens *et al.* 1967), take place in two stages, affecting decidual and myometrial segments respectively and are normally completed by 22–24 weeks gestation (Pijnenborg *et al.* 1981; Robertson *et al.* 1986) and allow for the necessary increase in blood flow as pregnancy progresses.

The remarkably astute observation by Brosens *et al.* (1972) that the myometrial segments did not undergo these physiological changes in pre-eclampsia, eclampsia or a proportion of fetal growth retarded pregnancies has since been confirmed by and large by other workers studying different ethnic populations in other centres (Sheppard & Bonnar 1976; Althabz *et al.* 1985; Robertson *et al.* 1986; McFadyen *et al.* 1986; Frusca *et al.* 1989; Moodley & Ramsaroop 1989). Part of the disagreements result from a general lack of uniformity of definition of the clinical conditions, such as pre-eclampsia and intrauterine growth retardation. Recently in this journal Pijnenborg *et al.* (1991) re-examined the morphology of the placental bed arteries and related them to the new classification of the hypertensive disorders of pregnancy proposed by Davey & MacGillivray (1988). This and other papers emphasize the fact that some uncertainty still exists in the morphology of the placental bed.

The minor disagreements pertain to the difficulties in the interpretation of placental bed biopsies and to inherent problems associated with sampling. Some of these aspects have been reviewed by Robertson *et al.* (1986) but it is worth reiterating the difficulty in confirming that a biopsy has indeed derived from the placental bed. The finding of physiologically converted spiral (uteroplacental) arteries, whether in the presence or absence of interstitial trophoblast, is convincing evidence for a biopsy having derived from the placental bed. It can be argued that a biopsy containing interstitial trophoblast is derived from the placental bed and the converse

where no interstitial trophoblast is seen has come from outwith the placental bed. But what is to be made of the biopsy containing interstitial trophoblast but showing absent physiological changes in the spiral artery? Has it derived from the placental bed or from the margin? To be confident of excluding the latter, the presence of plentiful interstitial trophoblast is a useful aid as the density of extravillous trophoblast infiltration into the placental bed fades towards the periphery (Pijnenborg *et al.* 1981). This may partly explain the reporting of interstitial trophoblast clustering around physiologically unconverted arteries in abnormal pregnancies (Gerretsen *et al.* 1983; Pijnenborg *et al.* 1991). In the past it has been assumed that where there are no physiological changes in the spiral artery and no surrounding interstitial trophoblast that the biopsy has come from outwith the placental bed but it is possible that interstitial trophoblast infiltration may be patchy, as suggested by morphological studies of the placental bed in miscarriages (Khong *et al.* 1987; Hustin *et al.* 1990). Finally, could trophoblastic giant cells be seen beyond the placental bed as suggested by Shanklin & Sibai (1989) or could those biopsies have come from under a succenturiate lobe or a small non-involuting cotyledon in the chorion laeve, where the vascular changes have not been adequately investigated? It is obvious from the foregoing that the difficulty of ascertaining if a biopsy is from the placental bed needs to be overcome before the interpretation of a complex structure can even be contemplated.

Notwithstanding these diagnostic difficulties, the most easily discernible morphological feature of abnormal placentation, that is, absent trophoblast-induced physiological vascular changes, has been extended to include absence of physiological changes in decidual segments in those pregnancy disorders (Khong *et al.* 1986) and also in a proportion of miscarriages (Khong *et al.* 1987; Michel *et al.* 1990; Hustin *et al.* 1990). The finding of a similar defect in decidual segments as well as in first trimester miscarriages suggests that too much emphasis has been placed previously on the failure of the second wave of endovascular trophoblast migration and that it may be an overall defect in endovascular trophoblast migration that results in inadequate haemochorial placentation. Furthermore, the clustering of interstitial trophoblast around spiral arteries in early pregnancy and their deficiency in miscarriage suggests that there is a

temporal window when interstitial and endovascular trophoblast must migrate and interact with the spiral arteries outside which defective placentation will result (Khong & Sawyer 1991). In placenta accreta, the process may be too vigorous with physiological changes affecting even radial and arcuate arteries while abnormalities in the interstitial trophoblast population have been described also (Khong & Robertson 1987).

These morphological observations have led Robertson *et al.* (1985) to suggest that abnormal haemochorial placentation may be a common feature in a variety of pregnancy disorders. Their hypothesis that the integrity of the maternal blood supply to the fetoplacental unit is important for pregnancy success is supported further by some recent clinical observations.

Failure to establish an adequate sustaining uteroplacental circulation consequent upon an aberrant haemodynamic uterine blood supply may result in pregnancy failures. Women with an anomalous bifid ascending uterine artery, especially if bilateral, had a significantly higher miscarriage rate and had lower birthweights of infants from successful pregnancies when compared with women with a normal single ascending uterine artery (Burchell *et al.* 1978). Primary arteriovenous malformations of the uterus are rare but a review of 16 reported cases showed eight associated with previous miscarriage, including one patient with a history of recurrent abortions (Fleming *et al.* 1989).

There is an increased occurrence of low birthweight infants and miscarriages in women who had been treated previously by abdominal or pelvic irradiation for childhood tumours, such as Wilm's tumours, compared with those not treated by irradiation (Li *et al.* 1987; Smith & Hawkins 1989). A recent case report of placenta percreta associated with a second trimester abortion in a patient with previous pelvic irradiation highlights this problem further (Pridjian *et al.* 1990). The most likely explanation is that radiation in some way alters the intrauterine vasculature such that subsequent physiological changes are impaired (Smith R. A. and Hawkins M. M., personal communication). It is noteworthy that in experimentally irradiated animals, intimal thickening, medial fibrosis and obliteration of the lumen by foam cells are seen in the uterine vessels (Kraus 1973), a lesion not unlike the vasculopathy, acute atherosclerosis, that is seen in uterine vessels in pre-eclampsia and intrauterine fetal growth retardation (Labarrere 1988; Khong 1991).

The mean birthweight of full term infants born to mothers with primary Raynaud's phenomenon, a systemic vasospastic disorder, was significantly less than that born to controls suggesting that vasospasm in uterine vessels could lead to subtle placental compromise (Kahl *et al.* 1990). There is no doubt that there can be vasospasm in the unconverted placental bed spiral arteries in the pregnancies complicated by hypertension (see illustration in Robertson *et al.* 1986) but the morphology of the placental bed vessels in Raynaud's phenomenon has not been described and whether there is autonomic neural control in physiologically altered vessels is unclear. Evidence to date suggests that the uterus is denervated during pregnancy (Thorbert *et al.* 1979; Morizaki *et al.* 1989) although there are dissenting views (Zuspan *et al.* 1981). The roles of endothelium, and of endothelin-1 in particular, in local control of blood flow in Raynaud's phenomenon (Zamora *et al.* 1990) and in pre-eclampsia (Taylor *et al.* 1990) have been raised and clearly need to be dissected in the light of placental vasculature morphology.

Given that successful haemochorial placentation is an important determinant in pregnancy outcome, assessment of the uteroplacental circulation may be a useful adjunct to current antenatal tests of uteroplacental well-function. Interest has rightly focused on the use of Doppler ultrasound, including colour-flow Doppler systems. Unfortunately, while a good correlation exists between resistance index from Doppler flow velocity studies of the uterine arteries and the morphology of the placental bed spiral arteries (Khong *et al.* 1984) other factors such as maternal plasma volume (Steel *et al.* 1990) and blood pressure (Gerretsen *et al.* 1981) clearly interact in determining flow.

It is some 34 years since chance threw Dixon, a British obstetrician who was fascinated by the local high incidence of pre-eclampsia, and Robertson, a pathologist with a growing reputation in cardiovascular pathology, together in Jamaica (Robertson *et al.* 1984). They devised a method of sampling the placental bed (Dixon & Robertson 1958) that has generated a remarkable insight into the importance of adequate haemochorial placentation in human pregnancy by allowing large numbers of cases to be studied. In stimulating these developments as well as providing biopsy material for attempts to elucidate features of materno-trophoblastic interaction that allow or restrain trophoblast migration and,

hence, an understanding of the placentation process, the perspicacity of Robertson, Brosens and Dixon cannot be gainsaid.

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Elective section after two sections—where's the evidence?

Many clinicians agree that an elective caesarean section at term is necessary when a woman has been delivered twice by caesarean section. It is generally assumed that there is a considerable weight of historical evidence in favour of this management but close inspection of the relevant publications reveals a plethora of unsupported personal opinion quoted, misquoted and paraphrased until the rule 'twice a section always a section' has become ingrained within our practice.

One of the earliest authors providing us with an unsupported opinion was O'Donel Browne (1951) who said that the woman who has already had several lower segment operations runs an increasingly greater risk of rupture if submitted to labour, for the unavoidable formation of scar tissue at the site of operation weakens the lower segment. Two years later Harris (1953) said that he rejected patients (from a trial of labour) who

gave a history of several previous caesarean sections, believing that repeated assaults on the uterine musculature were not conducive to the formation of strong scar tissue. His opinion was quoted by Lavin *et al.* (1982) and Tahilramaney *et al.* (1984) without reference to his lack of supporting data. The opinion seemed a popular one, Kaltreider & Krone (1959) stated, again without evidence, that vaginal delivery after more than one caesarean section was 'not generally recommended'. Even as recently as the last decade personal opinions have abounded, O'Sullivan *et al.* (1981) laid down their unsupported criteria for allowing a trial of scar, their first being that the patient should have only one scar, Flamm *et al.* (1984) felt that more than one previous caesarean section was a contraindication to a trial of labour but produced no supporting evidence, Bider *et al.* (1990) stated that: 'We do not allow patients

with two previous caesarean sections to deliver vaginally', but had to admit that this policy was quite arbitrary.

Examples exist whereby authors who made no mention of women with more than one section are later quoted as having given an authoritative opinion on the subject, e.g. Pauerstein *et al.* (1969) are reported by Lavin *et al.* (1982) as having said that they believed having more than one section increased the risk (of scar rupture), in fact Pauerstein *et al.* (1969) made no mention of such women.

McGarry (1969) is quoted by Lavin *et al.* (1982) in that he believed there to be an increased risk associated with more than one previous section. In fact McGarry (1969) acknowledged previous work illustrating the safety of such a labour and allowed two such women to do so. He did write: 'it seems reasonable that patients who have had two previous sections should not be submitted to the anxieties attendant on attempts at vaginal delivery especially since the attempt may be unsuccessful because of inefficient uterine action or fetal distress even if scar rupture does not occur'. His concern for the feelings of pregnant women is laudable, his paternalistic attitude questionable.

When figures have been produced, some have been interpreted in a most unusual manner; Donnelly & Franzoni (1964) reported a series of 219 755 deliveries containing an unknown number of patients with a caesarean section scar. They argued that because four out of every 10 ruptures of caesarean section scars that occurred before labour did so in women with more than one scar, 'this statistic reaffirms the necessity for elective repeat caesarean section in any patient who has had more than one section'. Later the same authors (Donnelly & Franzoni 1967) produced guidelines for the selection of patients for trial of scar. Their first was that 'any patient who has had more than one caesarean section . . . should be excluded from consideration for vaginal delivery'. This was after reporting a series of 2904 patients with between one and four section scars, who suffered 13 ruptures (five of these before labour) of which three occurred in those with more than one scar. There is no logical connection between the statistics presented and the conclusions drawn.

Case *et al.* (1971) reported an almost identical uterine rupture rate of 0.69% in 1259 and 0.67% in 297 women with one and two caesarean section scars respectively. Porreco & Meier (1983)

cited this as a comment on the safety of allowing a trial of scar to occur. Besides failing to note the practically identical incidence of scar rupture in women with two scars as compared with those with one, they failed to report that the work by Case *et al.* (1971) was on findings at elective caesarean section and made no reference to the safety of trials of scar.

Tahilramaney *et al.* (1984) quote Schmitz & Gajewski (1951) as saying that multiple scars predispose to uterine dehiscence, Schmitz & Gajewski (1951) had reported a rupture rate of 1.1% among 128 with two scars and 1.9% amongst 320 with one scar, but had made no mention of the relative proportions of each group electively sectioned. The same paper also quotes Pedowitz & Schwartz (1957) as saying the same thing, albeit to a degree that was not statistically significant, when their figures did not include trials of scar.

As the number of references containing advice has mounted, clinicians have naturally shied away from allowing these women to be delivered vaginally. Together with the intention of reporting homogeneous groups when publishing series of trials of scar this has led to researchers excluding such women from their prospective series. Later researchers have then tended to automatically assume that this was because of a proven concern about the rate of uterine rupture. For example, Lavin *et al.* (1982) reported that Gibbs (1980) believed that the presence of more than one scar increased the risk of uterine rupture but, in fact, Gibbs merely excluded such women from his series of deliveries, he gave no reasons why.

There is no conclusive proof of an increased risk of scar dehiscence during labour after two caesarean sections and the manner in which we have come to believe that there should be an embarrassment to all who consider obstetrics to be a scientific speciality. Enlightened authorities, albeit frequently responsible for the perpetuation of the myth in their references to the literature, have presented what is now a considerable weight of evidence that labouring with two scars is no more of a risk than with one. More importantly from the clinical viewpoint, they have failed to show any advantage from an elective abdominal delivery in these cases (Novas *et al.* 1989; Phelan *et al.* 1989; Hansell *et al.* 1990). Early work is marred by poor methodology and a high prevalence of classical section scars amongst study populations and previous

reviewers have noted how the relevant figures are often irretrievable from series reporting overviews of vaginal birth after caesarean (VBAC) (Enkin 1989). Arriving at a completely satisfactory summary of the facts is further hampered by varying study populations, selected for vaginal delivery upon different criteria, managed differently in labour for varying amounts of time. Terminology regarding scar complications also varies.

Even so, the current literature records the paucity of scar complications arising from attempts at a vaginal delivery. Novas *et al.* (1989); Phelan *et al.* (1989) and Hansell *et al.* (1990) have recorded between them 557 trials of scar in women having had two caesarean sections, 11 dehiscences were diagnosed, no maternal or fetal mortality resulted. The same three series all report a higher dehiscence rate at elective caesarean section allowing one to make the inference that the presence of asymptomatic and presumably bloodless scar defects is not being diagnosed following successful vaginal delivery.

The vaginal delivery rates from trials of scar after two caesarean sections are consistently high, despite exclusion categories set by authors which vary qualitatively and hence quantitatively in the percentage of women with two scars allowed to labour. Figures range from 69% (Phelan *et al.* 1989) to 82% (Stovall *et al.* 1987).

The potential for a vaginal delivery is partially preserved even if one of the patients' previous deliveries was for cephalopelvic disproportion/failure to progress/dystocia; 78% (Porrecco & Meier 1983), 70% (Farmakides *et al.* 1987) and 50% (Hansell *et al.* 1990) are typical statistics. Phelan *et al.* (1989) was even able to achieve a 56% vaginal delivery rate in those who had had two caesarean sections for cephalopelvic disproportion (CPD), this figure compares favourably to the 67% vaginal delivery rate described by Rosen *et al.* (1990) in their meta-analysis of labours after one section for CPD. It must also throw some doubt on the very existence of CPD as a necessarily recurrent phenomenon as a proportion of these infants were larger than their predecessors.

Obstetricians should remember that to allow a patient to labour is not a treatment, it is a virtually unavoidable consequence of pregnancy. If we are to perform a surgical procedure in order to circumvent labour we should have a clear indication. The historical evidence does not pro-

vide one and current publications indicate that we do not appear to benefit our patients by delivering them electively by caesarean section.

We would do well to attend the words of Bertrand Russell (1957): 'If you have an opinion about any matter it should be based on ascertained facts, not upon hope, or fear, or prejudice'.

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Abortion in Poland

When I write these words, the beginning of July 1991, abortion is still legal in Poland. Two years of passionate discussion and debates have not concluded in any unequivocal resolution. On 15 June the lower house of the Polish Parliament (Sejm) decided to adjourn the debate. The abortion bill, argued members of Parliament from the Democratic Union Caucus—a new party which emerged from the right wing of the former Solidarity—is too fundamental an issue to be accepted in haste. It ought to be a complex document covering all issues concerning maternity and institutional care for unborn and unwanted children. The good—argued Mrs J. Hannelowa, a journalist from the Catholic *Tygodnik Powszechny* and a member of Parliament—must be done well. The first item on the parliamentary agenda is now a new general election procedure. In the autumn the Poles are to elect the first really democratic Parliament. It seems evident that politics is much more important than abortion. However, from the very beginning until its quite unexpected culmination in June, the Polish

controversy on abortion was a classical example of political conflict. Nobody cared about any subtle moral or metaphysical arguments. It was evident that who wins the abortion debate will control the political situation in Poland.

This is how the issue began. Since 1956 there has been a law in Poland which permits a woman to have an abortion for medical and social reasons, and when conception is the result of rape. The 'social reasons' clause is flexible enough to cover all cases when abortion is performed for reasons other than rape or medical indications. In fact, until recently the present law allowed an abortion on demand and without a set time limit, though it was established custom not to perform it beyond the first trimester. When in the late 1980s the Solidarity movement recovered from the blows inflicted by martial law it had changed its tactics of political fighting. It was no longer the frontal attack against existing law and political institutions with spectacular strikes and street rallies. It was simply support for all forms of political dissatisfaction in the

country. I do not claim, of course, that it was the Solidarity leaders who decided to raise the question of abortion. But when in spring 1989 a group of Catholic intellectuals from Wrocław prepared a draft of the new abortion law it suddenly got quite strong support from the Church and right wing circles of Solidarity. It was argued that the existing Abortion Act was a shameful relic of the Communist regime and a symbol of the Soviet domination. It was argued that it was a mortal threat to 'the biological substance of the nation' and that the total overcoming of the Marxist and Communist heritage in Poland demanded abolishing the old law and imposing a total ban on abortion.

Indeed, the new draft of the abortion law called 'On legal protection of the conceived child' was very radical. The core of the proposed new legislation was the section in which it has been declared that 'each human being has a legal capacity from the moment of conception'. Hence: 'who causes death of the conceived child is subject to punishment of up to three years deprivation of liberty.' This meant in fact that each woman and each doctor involved in the performance of an abortion would risk up to three years in jail. The proposal, which was overtly inspired by, and received very strong backing from, the Roman Catholic Church, stirred up unprecedented debate in the mass-media, churches, universities, and even in educational institutions.

The government seemed deliberately to avoid taking sides in the controversy. This led some observers to speculate that the abortion controversy was really to the advantage of the State and the ruling Communist party because it was expected that it would discourage women from casting their votes for the Church-supported Solidarity candidates.

In the last two years, after a total collapse of the Communist regime in Poland, the Polish Parliament has been debating four different drafts of the new law on abortion. The first three (Wrocław project, the President's of the Senate project and the Senate commission project) were unanimous in radical condemnation of abortion. They have differed only with regard to whether a woman should be prosecuted for undergoing an abortion, how many years in jail a doctor performing an abortion and his accomplice should spend, and whether the new law should allow for any exceptions (e.g., in case of rape, congenital handicaps of the fetus or when pregnancy

endangers the life of the woman). The fourth project proposed by a group of liberal members of Parliament in March this year, although condemning abortion as a method of family planning, nevertheless allowed for termination of pregnancy in such cases as danger for the health or life of the woman, congenital conditions of the fetus, rape, or some serious social reasons.

At present the situation is rather odd. The old law has not been abolished but it is much more difficult to have a legal abortion than a year or two ago. On 30 April 1990 the Minister of Health and Social Care issued a new executory provision to the Abortion Law of 1956. According to these regulations if a woman requests abortion for social reasons she must provide the doctor with a *written* declaration of her intention and the doctor, after explaining the harmful effects of abortion, *should try to discourage her* from it. If the woman still insists on abortion the doctor should consult another specialist and should request from her a certificate that she has been interviewed by a certificated psychologist about her life conditions and reasons for wanting an abortion. If there are no medical reasons for abortion, if the doctor is not persuaded by the arguments of the woman about her difficult life situation, or if the pregnancy continues more than 12 weeks, then the woman cannot demand an abortion.

In summer last year there was only one gynaecological ward in Warsaw with a psychologist working full-time and most of the Polish psychologists feel they are not properly qualified to advise on abortion issues.

It is difficult to predict the results of the next ballot on the abortion bill as it depends on the political situation in Poland which is far from stable.

The Church, perhaps the best organized and most powerful political force in Poland, claims that the State should not be separated from the Church. The Polish bishops demand that the constitution should declare the right to life from conception as well as the right to religious education in every kind of school. (In fact since October last year the Catholic religion is taught in all schools and kindergartens). 'We believe', say the Polish bishops, 'that the time has come when we must reject the false and harmful belief—which unfortunately is grounded in social consciousness—that a secular state is perceived as the only and fundamental guarantee of freedom and equality of the citizens' (Gazeta

wyborcza, 25 April 1991). If the Church succeeds in maintaining its moral and political supremacy in Poland it will mean not only a total ban on abortion but also a ban on selling contraceptives. (The IVF programmes have been already suspended.)

On the other hand, the State is too weak and inexperienced to oppose or mediate between different pressure groups. For more than 40 years of Communist oppression in Poland the Church was indeed immensely important in the fight to protect and preserve the national identity. Many politicians from the new political parties refer now to Christian social ethics and the moral authority of the Church simply to gain the Church's blessing and political support of the electorate. In fact, before the general election in summer 1989, the abortion issue was a kind of litmus paper for most candidates. If they were pro-choicers it was interpreted as support for the Communist regime.

There is also a problem of how to protect the rights of minorities. One cannot, of course, treat women as a minority. But in fact they do not have much say in the present debate and their protests are simply ignored. The women's liberation movement did not get through to Eastern Europe. Many Catholic members of Parliament would rather see women stay at home and look after children.

The situation of the medical profession is particularly difficult. Though the Polish Medical

Association decided not to take any official position in the debate, considering it a question of conscience, nevertheless there is strong pressure to withhold abortion from the State hospitals and clinics. In May 1990, referring to the April instruction of the Ministry of Health, the medical staff of the Institute of Gynecology and Obstetrics at the Medical Academy in Cracow decided not to perform abortions. Women may, of course, have an abortion outside the national health care system but when it is performed on a private basis it costs up to US\$80. The starting salary for a young teacher is approximately US\$110 per month. A competent and well-informed person told me recently that we may soon expect a special instruction from the Ministry of Health forbidding any abortions in private surgeries.

Whatever is the final decision of the Sejm, one thing is absolutely certain: it is a bad time for Polish women. It is also a bad time for those of the medical profession who are responsible for women's health.

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Erythrocyte hydration in normal human pregnancy

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Abstract

Objective—To determine whether the fall in plasma osmolality in normal human pregnancy resulted in cellular overhydration.

Design—The changes in erythrocyte hydration, potassium and total osmoles in response to a decrease in osmolality *in vitro* and associated with the fall in plasma osmolality in normal pregnancy were determined.

Subjects—Fifty-one women were studied serially during pregnancy and again 20 weeks after delivery.

Results—Erythrocytes from pregnant women exposed *in vitro* to a 29.9% osmolality decrement had a 28.5% increase in cell hydration. At 14 weeks gestation although plasma osmolality was lower than after delivery (281.1 vs 291.6 mosmol/kg; $P < 0.001$) both erythrocyte hydration (1.83 l/kg dry weight cells) and potassium (264 mmol/kg) contents were reduced from the nonpregnant values (1.88 l/kg; $P < 0.01$; 272 mmol/kg; $P < 0.001$). For the remainder of pregnancy plasma osmolality remained at this lower level but cell hydration and potassium both increased to values at 38 weeks gestation that were greater than in the nonpregnant state (1.92 vs 1.88 l/kg, 287 vs 272 mmol/kg).

Conclusions—These findings suggest that a loss of cell osmoles may be a primary event affecting cell hydration in pregnancy and plasma osmolality is then reduced to maintain normal cell hydration. Subsequent changes in cell hydration were led by changes in intracellular osmole content.

All cells are freely permeable to water and therefore there is osmotic equilibrium across the cell membrane (Macknight & Leaf 1977; Macknight

1985; Alberts 1989). Plasma osmolality is normally controlled within narrow limits, presumably to ensure constant cellular hydration. However, normal human pregnancy is characterized by a reduction in plasma osmolality of 10 mosmole/kg, which is significant by 10 weeks gestation and maintained until term (Davison 1981; Lindheimer *et al.* 1989). This hypo-osmolar plasma must be at osmotic equilibrium with the intra-erythrocyte contents so that either an increase in cell water or a reduction in intracellular osmotic content could be expected during pregnancy (Durr 1989).

The resetting of the osmostat is perceived as normal by the pregnant woman and she drinks and excretes a water load normally (Davison 1984) which may indicate that cellular hydration is also normal. It is interesting that pathological evidence indicates that a reduction in plasma osmolality may accompany a reduction in cell

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osmolytes, particularly potassium (Flear & Singh 1973). If the hypo-osmolar plasma in pregnancy is inappropriate for cell hydration then we would expect to find an increase in cell hydration, as we have found in hyponatraemia (unpublished observations); if it is appropriate for cell hydration because of a loss of cell osmolytes, then cell hydration should be normal.

Cellular hydration is difficult to measure under *in vivo* conditions but erythrocytes are uniquely suited to this purpose. Erythrocytes can be rapidly collected from whole blood without washing so that they are maintained under *in vivo* conditions as far as possible. Some authors have reported evidence that young erythrocytes can compensate for the swelling caused by a decrease in external osmolality by reducing their osmolyte content, probably mainly potassium (Ellory & Hall 1988; O'Neill 1987). However, mature human erythrocytes do not have the ability to cope with marked fluctuations in external osmolality by adjusting their internal osmolyte content (Ellory et al. 1986; Brugnara 1987). Therefore, when exposed to a hypo-osmolar solution, mature human erythrocytes will swell with an increase in cellular hydration. This response has been studied *in vitro* with artificial manipulation of external osmolality (Solomon 1971). Therefore the changes in erythrocyte hydration, total osmoles and potassium contents, may be useful in giving an insight to the osmolality changes during human pregnancy.

This study was undertaken to determine whether there was a change in erythrocyte hydration or total osmolyte content, or both, associated with the osmolality decrement in normal human pregnancy. Because there is some doubt about the importance of erythrocyte age in the response to osmotic changes, both young and mature erythrocytes were studied.

Subjects and methods

Normotensive primigravid pregnant women with uncomplicated singleton pregnancies were studied serially at 14, 20, 26, 32, and 38 weeks gestation, and again 20 weeks after delivery, when they acted as their own nonpregnant controls. No woman was taking any medication other than iron supplementation in the second half of pregnancy (4 subjects). Ethical approval was obtained from the joint ethics committee of Newcastle Health Authority and the University of Newcastle-upon-Tyne, verbal consent was

obtained from the women. Sixty women were enrolled in the study, of whom 51 had a normal pregnancy. The data from these women were used for analysis.

With the woman in a semi-recumbent position for 20 min, a 20 ml sample of blood was collected from an antecubital vein into tubes containing lithium heparin. Analyses were undertaken within 2 h of collection. Blood samples were centrifuged at 2000 *g* for 3 min at 4°C, plasma was removed and the buffy coat was discarded. The plasma osmolality was measured in duplicate by freezing point depression on a Camlab osmometer (Camlab Ltd, Nuffield Road, Cambridge, England).

The packed erythrocytes were not washed but kept in maternal plasma so that conditions were maintained as close as possible to those *in vivo*. They were transferred to 6×45 mm polythene tubes and centrifuged at 15000 *g* for 15 min in a fixed angle centrifuge head as described by Murphy (1973). Adjacent slices were then taken from the top and middle 10% of the tube to give respectively young and mature erythrocytes. In each case one slice was weighed before and after drying to constant weight in an oven at 50°C for 24 h. The cell hydration was calculated from the change in weight as litres/kg dry cell weight. The other slice was also weighed before disruption in 4 ml of 1.5 mmol/l CsCl containing 0.1% Triton X-100 and the potassium concentration was measured using an IL943 flame photometer (Instrumentation Laboratory, Warrington, England). The erythrocyte potassium was expressed as mmol/kg dry cell weight. Measurements of hydration and potassium each had a coefficient of variation of 1%.

To demonstrate that this technique could reliably measure differences in erythrocyte hydration, we undertook a preliminary *in vitro* study to measure the response of erythrocytes from pregnant women to a change in external osmolality. Four 1 ml aliquots of red cells from four pregnant women were washed and incubated in 2 ml of MgCl₂ at one of four different osmolalities (230, 261, 288 and 328 mosmole/kg) for 10 min at 37°C and then handled as described above.

Although plasma osmolality is usually expressed as mosmole/kg of water this is equivalent to 1 litre of water at 25°C. At room temperature the reciprocal of osmolality can then be used to derive the volume of water associated with each mosmole. The value of ml of water/

mosmole was calculated from 1000/plasma osmolality. Since the value in plasma must equal that in cell water then, as both cell water and plasma osmolality are known, they can be used to calculate the total cell osmole content (mosmole/kg dry cell weight). The contribution made to the total cell osmole content by potassium can then be calculated.

Statistical analysis was performed using the SPSS-PC (v3.1) package (SPSS Inc. 444N. Michigan Avenue, Chicago, Illinois 60611) and results are expressed as mean (SE) of all data obtained at each visit. Some subjects were unable to attend all visits and this accounts for the small variation in the numbers studied at each time point. We have used the regression coefficient for each variable with time as a summary measure of the changes occurring during pregnancy (Matthews *et al.* 1990). Student's *t*-test for paired data was then used to test for a significant difference in the mean of the regression coefficients between the times of interest. This approach to the analysis of serial data in pregnancy, deriving a summary measure of the changes with time, has been used before (Pitkin *et al.* 1979) and in this way we have avoided the potentially misleading effect of multiple comparisons on repeated measurements during pregnancy.

Results

Exposure of the erythrocytes to a range of external osmolalities representing a 29.9% decrement in osmolality (Fig. 1) resulted in the

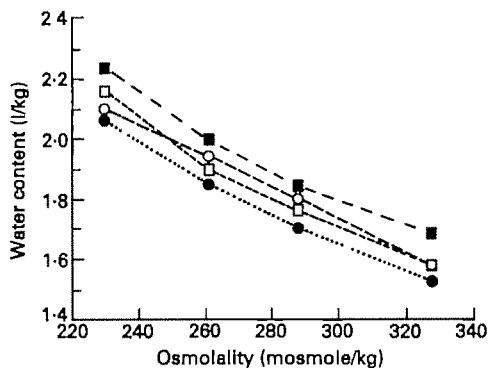


Fig. 1. The effect of changing external osmolality on the water content of erythrocytes from four pregnant women.

anticipated increment in cell hydration (28.5%), but no change in the cell potassium content (Fig. 2) suggesting that erythrocytes from pregnant women behave in the same way as erythrocytes from nonpregnant women under *in vitro* conditions. This method of measurement of cell hydration is appropriate for the detection of changes in hydration in response to a change in external osmolality.

Plasma osmolality was lower at 14 weeks gestation than in the nonpregnant state and erythrocyte hydration was also lower at this time (Table 1). This change was accompanied by a decrease in total cell osmole content (Fig. 3). Although the erythrocyte potassium content decreased it appeared that a reduction in other cell osmoles also contributed to the lower total cell osmole content. But at 14 weeks gestation the erythrocyte potassium content was a significantly greater proportion of the total cell osmole content than it was in the nonpregnant state (Fig. 4).

The mature erythrocytes had lower hydration, total cell osmoles and potassium than the young cells (Table 1), although the differences between nonpregnant and 14 weeks gestation were similar or slightly greater in mature than young erythrocytes.

Between 14 and 38 weeks gestation, plasma osmolality remained constant at a value lower than in the nonpregnant state. Erythrocyte hydration increased over this period from its low value at 14 weeks gestation to a value at 38 weeks gestation that was slightly greater than nonpregnant values (Table 1). This increase in cell hydration was accompanied by a marked rise in total intracellular osmoles but no change in plasma osmolality. These changes appeared to take

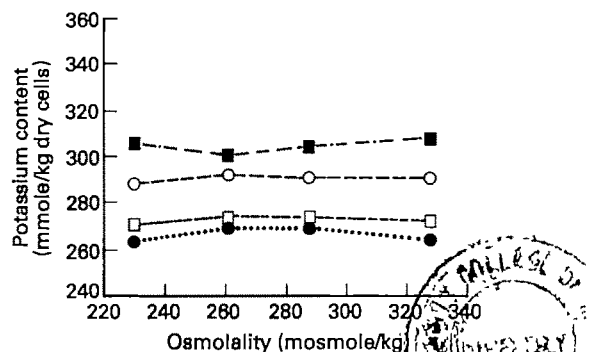


Fig. 2. The effect of changing external osmolality on the potassium content of erythrocytes from four pregnant women

Table 1. Plasma osmolality and erythrocyte water, potassium and osmole content during pregnancy and after delivery in young and mature erythrocytes

Variable	Gestation (weeks)						Regression coefficients	
	NP	14	20	267	32	38	NP-14	14-38
<i>Young cells</i>								
Plasma osmolality (mosmole/kg)	291.6 (0.9)	281.1 (0.5)	279.9 (0.5)	280.9 (0.4)	280.7 (0.4)	281.7 (0.4)	-0.76 <i>P</i> <0.001	0.014 n.s.
Total erythrocyte osmoles (mosmole/kg)	550 (3)	515 (6)	513 (4)	522 (5)	530 (4)	541 (4)	-2.66 <i>P</i> <0.001	1.21 <i>P</i> <0.001
Erythrocyte water (l/kg dry weight)	1.88 (0.01)	1.83 (0.02)	1.83 (0.01)	1.85 (0.02)	1.89 (0.01)	1.92 (0.01)	-0.0041 <i>P</i> <0.01	0.004 <i>P</i> <0.001
Erythrocyte potassium (mmol/kg dry weight)	272 (2)	264 (2)	268 (2)	270 (2)	277 (2)	287 (2)	-0.58 <i>P</i> <0.002	0.91 <i>P</i> <0.001
Total osmoles other than K	278 (2)	251 (4)	245 (2)	252 (3)	254 (2)	254 (3)	-1.8 <i>P</i> <0.001	0.37 n.s.
Potassium % total osmoles (%)	49.5 (0.2)	51.4 (0.4)	52.2 (0.3)	51.9 (0.2)	52.2 (0.3)	53.0 (0.2)	0.14 <i>P</i> <0.001	0.057 <i>P</i> <0.01
<i>Mature cells</i>								
Total erythrocyte osmoles (mosmole/kg)	518 (3)	478 (5)	486 (4)	484 (4)	486 (4)	492 (3)	-3.02 <i>P</i> <0.001	0.57 <i>P</i> <0.01
Erythrocyte water (l/kg dry weight)	1.77 (0.01)	1.70 (0.02)	1.74 (0.01)	1.72 (0.02)	1.73 (0.01)	1.76 (0.01)	-0.0063 <i>P</i> <0.001	0.002 <i>P</i> <0.01
Erythrocyte potassium (mmol/kg dry weight)	252 (2)	239 (2)	246 (2)	244 (2)	246 (2)	256 (2)	-1.05 <i>P</i> <0.001	0.58 <i>P</i> <0.001
Total osmoles other than K	266 (2)	239 (3)	241 (3)	241 (3)	240 (3)	240 (3)	-1.97 <i>P</i> <0.001	0.08 n.s.
Potassium total osmoles (%)	48.6 (0.2)	50.0 (0.3)	50.6 (0.3)	50.4 (0.3)	50.8 (0.3)	51.6 (0.3)	0.1 <i>P</i> <0.001	0.05 <i>P</i> <0.002
Number	47	47	50	50	50	46		

Results are mean (SEM) values. NP represents non-pregnant values obtained at 20 weeks after delivery. The regression coefficients were calculated with respect to gestation and the probability of the slope being different to no change is shown. The regression coefficients between NP and 14 weeks were directly compared with those between 14 and 38 weeks using a *t*-test (**P*<0.05; ***P*<0.005; ****P*<0.001).

place between 20 and 38 weeks gestation. The change in intracellular osmoles was associated with an increase in erythrocyte potassium content, which by 38 weeks gestation was markedly higher than either after 14 weeks gestation or in the nonpregnant state. In contrast, cell osmoles other than potassium showed little change between 14 and 38 weeks gestation and remained lower than in the nonpregnant state. Therefore at 38 weeks gestation the erythrocyte potassium content was a greater proportion of the total cell osmoles than at 14 weeks gestation or in the nonpregnant state (Fig. 4).

The relative changes in erythrocyte osmoles, potassium and hydration between 14 and 38 weeks gestation were the same in the mature and the young erythrocytes. However, the hydration state and potassium content remained low for longer during gestation and the increase in potassium at 38 weeks gestation was less marked in the mature cells.

Discussion

In the pregnant women at 14 weeks gestation the lower plasma osmolality was not accompanied

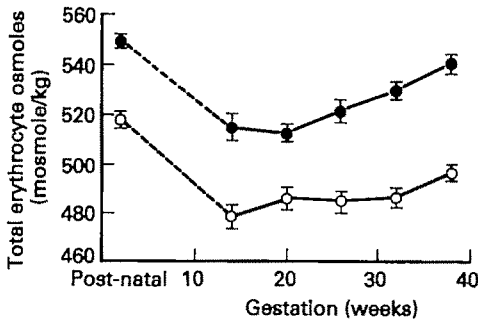


Fig. 3. The change in total erythrocyte osmole content during normal pregnancy. Data shown are mean and 1 SEM (○) mature erythrocytes, (●) young erythrocytes.

by an increase in erythrocyte hydration. Unexpectedly, there was a significant reduction in the cell hydration, an effect opposite to that predicted from the *in vitro* work where exposing erythrocytes to a lower external osmolality increased cellular hydration. The preliminary study confirmed that the technique which was used to measure erythrocyte hydration was able to measure differences in cell hydration in response to a change in external osmolality.

The technique used to measure erythrocyte hydration was chosen because of the possible variations to be found in erythrocyte size. Thus a large erythrocyte when normally hydrated may have a greater water content than a small erythrocyte that is overhydrated. In order to avoid such confusion in the interpretation of results the state of hydration was measured which is the ratio of water to cell solids and is independent of cell size. This approach assumes that an increase in cell solids implies a larger cell that will require an increase in water content to maintain normal cell hydration. Hence the ratio of cell water to cell solids would not change. This should be a better indication of cell hydration than the volume of water per cell or cell size.

It is well established that there is osmotic equilibrium across the cell membrane so that intracellular and extracellular osmolalities are identical (Macknight & Leaf 1977; Macknight 1985; Alberts 1989). Therefore when the plasma osmolality was reduced during pregnancy it is reasonable to assume that there was a comparable reduction in intracellular osmolality that could result from a gain of water or a loss of osmolytes by the cells. However, at 14 weeks gestation when the plasma osmolality was low,

the erythrocyte hydration was in fact significantly reduced which can only easily be explained by a loss of intracellular osmoles.

Although plasma osmolality is usually expressed as the number of milliosmoles associated with a kilogramme of water, this ratio can equally well be expressed as the volume of water associated with each milliosmole. As there is osmotic equilibrium across the cell membrane this value is the same through all body water, both intracellular and extracellular, except for the renal medulla. Since cell water, measured by weight, and cell osmolality were known, the units of water were compatible and it was possible to calculate the total cell osmole content. This was significantly lower at 14 weeks gestation than in the nonpregnant state. The decreased cell osmole content could be partly accounted for by a decreased potassium content, which is the major cationic intracellular osmole, but there was also a significant decrease in other intracellular osmoles. Furthermore, the increased ratio of potassium to total cell osmoles at 14 weeks gestation suggested a change in the osmotic composition of the cell. In the nonpregnant state potassium makes up 49.5% of the cell osmole content which increases to 51.4% by 14 weeks gestation and 53% by 38 weeks. To maintain electro-neutrality, potassium must be accompanied by anions and chloride is predominant, but the intra-erythrocyte chloride content is only of the order of 200 mmol/kg dry weight of cells (Funder & Wieth 1966). The remaining anions must be accounted for by organic and inorganic phosphates and other anions with a valency greater than one so that potassium does not have a one to one molar relation with its

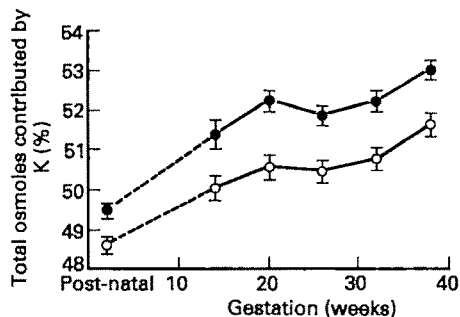


Fig. 4. The percentage contribution made to the total erythrocyte osmole content by potassium during pregnancy. Data shown are the mean 1 SEM (○) mature erythrocytes, (●) young erythrocytes.

anion. Therefore potassium contributes a correspondingly greater proportion of the cell's osmotic content than its accompanying anions, although this cannot be quantified unless the valency of the anions is known. The change in erythrocyte potassium in pregnancy was probably accompanied by a corresponding change in cell anions. Previous workers have also found that erythrocyte potassium and water content are reduced in pregnancy but they did not find an increase in potassium to greater than nonpregnant values at term (Herbinger & Wichmann 1967). However, that study was cross-sectional and studied different groups of ten women at six points in pregnancy comparing them with a different nonpregnant control group.

If the plasma osmolality in the pregnant women had stayed in the nonpregnant range with the same loss of cell osmoles there would have been a substantial decrease in cell hydration. Plasma osmolality may fall in pregnancy to prevent this cellular dehydration, which may compromise cellular function (Stuart & Ellory 1988). A recent review of maternal fluid adaptation to pregnancy (Durr 1989) alluded to the possibility that the red cell adapts to pregnancy by decreasing its solute content and suggested that a primary reduction in intracellular solute content may be responsible for the resetting of the osmostat in pregnancy. This hypothesis is supported by the data in this study. If the changes in pregnancy are a cell led phenomenon, presumably related to altered cell metabolism, and the change in plasma osmolality occurs to maintain an optimal intracellular environment for cell function it may explain why the changes occur without disturbance to the cells. In pathological states the changes are initiated outside the cell which responds as best it can but ultimately cell function is compromised and results in clinical sequelae. Hence in hyponatraemic patients there are the anticipated changes in cell hydration and potassium which are predicted from the change in osmolality; the erythrocytes are responding to an external event.

Although there is some suggestion (Ellory & Hall 1988; O'Neill 1987) that young erythrocytes can compensate for cell swelling by the loss of osmoles, mainly potassium, this mechanism seems unlikely during pregnancy for two reasons. First, the observed changes were similar in both young and mature cells during pregnancy. If mature cells do not have volume

regulation they should have had a greater over-hydration in the reduced plasma osmolality of pregnancy than the young cells but there was no evidence of an increase in hydration in the more mature cells. Second, this volume regulatory mechanism requires stimulation by cell swelling, but by 14 weeks the erythrocyte hydration was reduced, suggesting cell shrinkage rather than swelling. It is difficult to comprehend a physiological control mechanism that would over-compensate to the extent that a consistent reduction in cell hydration would occur.

The increase in erythrocyte hydration between 20 and 38 weeks gestation back to non-pregnant values occurred with the continuing low plasma osmolality and was explained by an increase in total cell osmoles. This suggests that the total cell osmole content plays an important role in cell volume homeostasis during pregnancy and acts independently of the change in external osmolality. Unlike the decrease in cell osmoles up to 14 weeks gestation, the increase in cell osmoles between 20 and 38 weeks gestation could have been completely explained by the increase in erythrocyte potassium as there was no further significant change in the other cell osmoles. A change in total cell osmoles could occur because of altered metabolic activity within the cell. Changes in acid-base balance and erythrocyte metabolism are known to occur during normal pregnancy (de Swiet 1980; Rorth and Bille Brake 1971; Tsai & de Leeuw 1982). Cell potassium would be affected by changes in the cell anion content but would also be affected by membrane permeability and membrane potential (Palmer 1989). It is interesting that the fall in erythrocyte potassium at 14 weeks gestation was accompanied by a similarly marked fall in osmoles other than potassium whereas between 20 and 38 weeks gestation the change in potassium was much more marked than in the other osmoles. It is possible that membrane physiology in relation to the movement of potassium was different at these two stages of pregnancy in accordance with the known changes in circulating lipids during pregnancy (Fahraeus *et al.* 1985; Desoye *et al.* 1987). These observations suggest that cell osmole content may be important for the determination of cell hydration during pregnancy, and raise interesting questions about the reason for a low plasma osmolality as part of the adaptation to pregnancy.

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Insufficient remodelling of the uterine connective tissue in women with protracted labour

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Abstract

Objective—To investigate the association between a slow progress of labour and insufficient remodelling of the uterine connective tissue.

Design—An open comparative study.

Setting—Danderyd Hospital, Department of Obstetrics and Gynaecology, referral centre.

Subjects—Eleven women (study group) in oxytocin augmented labour but with an unripe cervix in whom vaginal delivery could not be accomplished and 12 women (normal labour group) in normally progressing spontaneous labour and a favourable cervix but who needed to be delivered by caesarean section due to signs of fetal distress.

Interventions—At caesarean section tissue specimens were obtained from the fundus, the isthmus and the cervix uteri

Main outcome measures—Collagen concentration and extractability, collagenolytic activity expressed as DNP-peptide hydrolytic activity and the concentrations of sulphated glycosaminoglycans (S-GAG) and hyaluronic acid (HA) in the tissue specimens.

Results—Statistically significantly higher concentrations and lower extractability of collagen in the isthmus and the cervix uteri was found in women with slow progress of labour compared with those with normal labour.

Conclusions—An insufficient remodelling of the connective tissue in the cervix and isthmus uteri may contribute to slow progress of labour.

Unlike the cervix—a connective tissue organ—the body of the uterus functions as a smooth muscle organ during labour, but it also contains considerable amounts of connective tissue. In the human uterus the proportion of connective tissue changes gradually from the fundus to the cervix

being highest in the cervix with a collagen content of about 80% (Danforth 1947; Granstrom *et al.* 1989; Rorie & Newton 1967; Schwalm & Dubrausky 1966). During pregnancy, and in particular just before onset of labour, the cervix undergoes a ripening process, clinically recognized as softening and dilatation of the cervical canal. This process corresponds to a reorganization of the cervical connective tissue (Uldbjerg *et al.* 1983a). During pregnancy and parturition the connective tissue in the body of the uterus is also remodelled but not as extensively as that in the cervix (Granström *et al.* 1989). The clinical relevance of this uterine ripening process for the onset and maintenance of effective labour has not been investigated.

The aim of this investigation was to study if pro-

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tracted labour could be associated with an incomplete ripening of the uterine connective tissue.

Subjects and methods

The study included 23 women in term labour who were asked to participate in the study before they were delivered by caesarean section either for failed progress in labour or fetal distress. Women with suspected fetal macrosomia and known abnormal pelvis were excluded from the study. All of them gave informed consent and the investigation was approved by the local ethics committee of the Karolinska Hospital.

Study group

Eleven of the women had to be delivered by caesarean section because of failed progress of labour and they formed the study group. Their mean age was 30.8 years (range 25–39) and their mean gestational age 40.7 weeks (range 37–43). Seven women were nulliparous; the other four were secundigravidae of whom one had had a previous normal vaginal delivery and three had been delivered by caesarean section, two for slow progress in labour and one for fetal distress. Of these 11 women, two had started labour by rupture of the membranes and nine by uterine contractions. All the women had a still unripe cervix and had been in active labour, defined by at least three contractions of 60 s duration within 10 min, for a mean of 21 h (range 18–30 h). In addition, all had been given intravenous oxytocin for augmentation of labour for at least 5 h before abdominal delivery (Table 1).

Comparison group (normal labour)

The other 12 women had a normal progress in labour, but they were delivered by emergency

caesarean section because fetal distress was suspected. They formed the comparison group. Their mean age was 30.5 years (range 21–39) and their mean gestational age 39.7 weeks (range 38–41). One woman had had a previous normal vaginal delivery. The remaining 11 were nulliparae. All but two women had a spontaneous onset of labour with contractions. The other two started their labour by rupture of the membranes and spontaneous contractions 5 and 6 h later, respectively. All started labour with a favourable cervix and showed adequate progress in labour, defined as a cervical dilatation of at least 1 cm/h (Table 1).

Sampling procedure

Tissue specimens were obtained as described previously (Uldbjerg *et al.* 1983a; Granstrom *et al.* 1989). During caesarean section, biopsies were taken from the fundus and the isthmus, abdominally, and from the anterior lip of the cervix, vaginally. The weight of the biopsies varied from 50 mg to 75 mg after the mucosa and/or peritoneum had been cut off. All biopsies were immediately immersed in liquid nitrogen and stored at -70°C until analysed.

Analytic methods

Collagen concentration and extractability. The biopsies were cut into pieces <2 mm and delipidated with acetone. They were initially extracted three times with 1 ml 0.5 M acetic acid and then three times with 1 ml 0.5 M acetic acid containing pepsin (1 mg/ml). Extractions (23 h) and centrifugations (1 h at 20 000 g) between these procedures were performed at 4°C . The material was hydrolyzed in 2 ml of 6 M HCl at 100°C for 17 h, lyophilized and estimated as hydroxyproline according to Stegeman & Stalder (1967).

Table 1. Clinical data for the two study groups, women with slow progress in labour and women with normal labour

	Slow progress (<i>n</i> = 11)	Normal labour (<i>n</i> = 12)	<i>P</i> value (<i>t</i> -test)	95% CI of difference
Age (years)	30.8 (25–39)	30.5 (21–39)		
No. of nulliparae	7	11		
Gestational age (weeks)	40.7 (37–43)	39.7 (38–41)		
Cervical dilatation (cm)	3.8 (2–10)	5.2 (2–10)		
Height (cm)	163.8 (4.1)	164.8 (6.7)	0.69	(–3.9 to 5.8)
Duration of established labour (h)	24.6 (4.7)	6.0 (3.6)	<0.001	(–22.3 to –14.9)
Birthweight (g)	3530 (636)	3374 (554)	0.54	(–672 to 360)

Results are mean (SD) or mean (range) values

Table 2. Collagen concentration (determined as hydroxyproline) in cervical and uterine tissue from term pregnant women with slow progress of labour and from women in normal labour

Tissue specimen	Hydroxyproline ($\mu\text{g}/\text{mg}$ wet weight)		P value	95% CI of difference
	Slow progress (n = 11)	Normal labour (n = 12)		
Fundus	7.72 (1.12)	6.53 (0.67)	0.06	(-2.45; 0.07)
Isthmus	7.73 (1.20)	6.29 (1.40)	0.02	(-2.60, -0.20)
Cervix	8.83 (1.56)	5.74 (1.28)	<0.001	(-4.80, -1.49)

Results are mean (SD) values (Student's *t*-test).

Collagenolytic activity. Extractions were performed essentially as described by Kitamura *et al.* (1980). The specimen was crushed by 10 tons pressure during cooling with liquid nitrogen and then homogenized in 13 volumes of 0.25% Triton X-100, 500 mM Tris, pH 7.3, containing 100 mM CaCl_2 in a TRI-R tissue homogenizer, S61, for 4 min at 3000 rev/min. The homogenate was centrifuged at 15 000 *g* for 20 min at 2°C, whereafter the supernatant was diluted with extraction buffer. The hydrolytic activity against DNP-peptide was then assayed as described by Masui *et al.* (1977). The incubation time was 2 h and the extraction buffer was used as blank. The activity was determined against a DNP-peptide (2,4-dinitrophenyl - Pro - Gln - Gly - Ile - Ala - Gly-Gln-D-Arg).

Glycosaminoglycans. The concentrations of hyaluronic acid and sulphated glycosaminoglycans

were determined as hexosamine concentration after drying, delipidation with acetone, papain digestion and purification on columns of DEAE-cellulose (Uldbjerg *et al.* 1983b; Antonopoulos *et al.* 1964).

Chemical reagents. Papain (twice crystallized, 16–40 BAAE units/mg) was purchased from Sigma Chemical Co, USA, DEAE cellulose ion exchanger (DE-52) from Whatman Ltd, UK, and 2,4-dinitrophenyl - Pro - Gln - Gly - Ile - Ala - Gly-Gln-D-Arg (DNP-peptide) from the Protein Research Foundation, Japan. All other chemicals were of analytical grade.

Results

Perinatal outcome

All but one baby in each group had a 5-min Apgar score of >7. Mean birthweight did not differ

Table 3. Percentage of collagen in two extracts and in the remaining pellet in cervical and uterine tissues from women with slow progress of labour and from women with normal labour

Tissue specimen	Slow progress (n = 11)	Normal labour (n = 12)	P value	95% CI of difference
Extractability in 0.5 M acetic acid (%)				
Fundus	1.16 (1.26)	0.71 (0.59)	0.48	(-1.81 to 0.92)
Isthmus	2.06 (2.47)	0.93 (0.63)	0.19	(-2.93 to 0.66)
Cervix	2.13 (2.01)	1.99 (1.71)	0.89	(-2.31 to 2.02)
Extractability in 0.5 acetic acid + 1 mg pepsin/ml (%)				
Fundus	93.9 (3.26)	92.6 (2.38)	0.47	(-5.14 to 2.54)
Isthmus	89.3 (74.4–94.6)	94.0 (89.1–98.0)	0.02	
Cervix	70.43 (5.36)	89.05 (5.03)	<0.001	(12.27 to 24.96)
Not extractable (pellet) (%)				
Fundus	4.94 (2.86)	6.7 (2.16)	0.28	(-1.64 to 5.16)
Isthmus	7.95 (5.25–24.3)	5.0 (0.95–9.8)	0.03	
Cervix	27.67 (5.95)	9.04 (4.01)	<0.001	(-24.13 to -11.93)

Results are mean (SD) values (Student's *t*-test) or where values were skewed the median (range) values (Mann-Whitney *U* test) are given.

Table 4. Collagenolytic activity expressed as DNP-peptide hydrolytic activity in cervical and uterine tissues from women with slow progress of labour and from women in normal labour

Tissue specimen	DNP-peptide hydrolytic activity (units/100 mg wet weight)		P value	95% CI of difference
	Slow progress (n = 11)	Normal labour (n = 12)		
Fundus	120 (46)	102 (54)	0.53	(-79 to 43)
Isthmus	175 (56)	156 (75)	0.54	(-82 to 44)
Cervix	339 (145)	305 (121)	0.61	(-171 to 103)

Results are mean (SD) values (Student's *t*-test).

between the two groups; 3530 g (range 2700–4860 g) and 3374 g (range 2440–4150 g) in the study and comparison groups, respectively (Table 1). In each group there was one breech presentation, the others were all cephalic.

Collagen concentration and extractability

Compared with the normal-labour group, the collagen concentration was significantly higher in biopsies from the isthmus and the cervix uteri in the group with protracted labour (Table 2). Not only the concentration of collagen but also the arrangement of the collagen fibrils differed, as demonstrated by a lower solubilization by pepsin in the isthmical and the cervical biopsies (Table 3). This finding indicates that the cervical tissue of women with protracted labour is more inelastic and stiff. In the fundus uteri the collagen concentration was higher in the study group than in the normal labour group but the difference was not statistically significant (Table 2). In fundus uteri specimens the collagen extractability was similar in the two groups (Table 3).

Collagenolytic activity

The collagenolytic activity measured as the hydrolytic activity against a DNP-peptide was higher in biopsies from all locations in women with protracted labour than in those with normal labour. However, the differences were not statistically significant (Table 4).

Glycosaminoglycans

The concentration of sulphated glycosaminoglycans quantitated as hexosamine did not differ significantly between the two groups but the concentration of hyaluronan was significantly lower in samples from the cervix uteri in women with prolonged labour (Table 5).

Discussion

Cervical ripening expressed as a remodelling of the connective tissue has been proven necessary for an uncomplicated vaginal delivery (Uldbjerg *et al.* 1983a). In addition insufficient cervical

Table 5. Sulphated glycosaminoglycans (S-GAG) and hyaluronic acid (HA) (determined as hexosamine) in cervical and uterine tissues from women with slow progress of labour and from women in normal labour

Tissue specimen	Hexosamine (µg/mg wet weight)		P value	95% CI of difference
	Slow progress (n = 11)	Normal labour (n = 12)		
S-GAG				
Fundus	0.18 (0.03)	0.16 (0.03)	0.25	(0.06 to 0.02)
Isthmus	0.18 (0.04)	0.15 (0.04)	0.25	(0.08 to 0.02)
Cervix	0.14 (0.01)	0.17 (0.03)	0.05	(0.001 to 0.06)
HA				
Fundus	0.12 (0.04)	0.14 (0.04)	0.56	(0.04 to 0.07)
Isthmus	0.11 (0.02)	0.12 (0.04)	0.54	(0.03 to 0.06)
Cervix	0.08 (0.02)	0.12 (0.02)	0.01	(0.01 to 0.06)

Results are mean (SD) values (Student's *t*-test).

ripening has been found to contribute to a delayed cervical dilatation during active labour (Ekman *et al.* 1986). The corpus and the cervix uteri constitute a functional unit but our knowledge of the co-ordination between the myometrial contractions and the cervical dilatation process is incomplete.

The results from this study indicate the importance of a sufficient ripening of the uterine connective tissue to accomplish an effective labour.

The high collagen concentration in combination with the low collagen solubilization indicate a suboptimal disarrangement of the collagen fibrils giving an inelastic and stiff tissue. This insufficiency may influence the myometrial activity in a negative way resulting in an ineffective labour. No increased collagenolytic activity was found in women with protracted labour.

The connective tissue composition in the fundus does not seem to differ between the two groups. This might emphasize the importance of the lower part of the uterus as well as an optimal ripening of the connective tissue for a normal labour.

It is well-known that other factors such as the presentation and the weight of the fetus influence the progress of labour. We found no such differences between the two groups.

Since the regulatory factors for the remodelling of the uterine connective tissue are not well-known we can only speculate about the process. Cytokines like interleukin-I and TGF- β are factors which influence the metabolism of the connective tissue and thus, may be involved in this process. Furthermore, inflammatory cells like macrophages, neutrophils, mast cells and eosinophils probably play an active role (Jungueira *et al.* 1980). Finally, the influence of hormones such as oestrogens, progesterone and prostaglandins on the connective tissue remodelling remains to be established. Therefore, future research along these lines is necessary to give an understanding of the molecular mechanism of the ripening process and its importance for a normal progress of labour.

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Fast-scan magnetic resonance imaging of fetal anomalies

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Abstract

Objective—To identify those congenital fetal anomalies, previously identified by ultrasound scanning, in which fast-scan magnetic resonance imaging (F-SMRI) would give additional information for the perinatal management of the infants.

Design—Observational clinical study.

Setting—Hospital Department of Obstetrics and Gynaecology/Resonance Research Centre.

Subjects—Seven women carrying eight fetuses in whom congenital abnormalities had been identified using ultrasound scans. The duration of the pregnancies was 28 to 39 weeks gestation.

Interventions—Fast-scan magnetic resonance imaging at between 28 and 39 weeks gestation.

Main outcome measures—Identification of fetal abnormalities.

Results and conclusions—F-SMRI was of limited value in the diagnosis of further assessment of fetuses with abnormalities of accumulation of tissue fluid. Renal anomalies were poorly identified unless associated with cystic formation of the kidney. Further study is required in the imaging of fetal central nervous system anomalies. Until echoplanar imaging is more widely available, MRI does not contribute to the diagnosis of cardiac anomalies. F-SMRI appears to be most useful in the diagnosis and management of soft tissue gastro intestinal abnormalities

The prenatal diagnosis of congenital abnormalities of the fetus is an important part of perinatal medicine. It is of advantage to neonatal care

units and paediatric surgeons to obtain maximum information in the antenatal period so that the best preparation can be made for the birth of the infant in optimum condition. In addition, the more information that can be gained about the abnormality before the delivery, the more accurate and effective is the counselling given to the couple.

Ultrasound scanning is the most commonly used imaging technique but there are some anomalies which are difficult to detect *in utero* and some patients in whom clear ultrasound images cannot be obtained. Magnetic resonance imaging (MRI) has been studied to assess its role in investigating fetal anatomy (Powell *et al.* 1988). Its application, however, has been limited by the length of time taken to obtain an image with resultant image degradation due to motion

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artefact. Fast-scan magnetic resonance (F-SMRI) imaging of the fetus has advantages over conventional MRI as the imaging times are greatly reduced, thus reducing motion artefact (Garden *et al.* 1988; 1991). The purpose of this study was to ascertain in which circumstances F-SMRI might give extra information about the abnormality which would assist in the management of the mother and her fetus.

Patients and methods

Seven women in whom fetal abnormalities were suspected or diagnosed by ultrasound examination were examined by F-SMRI between 28 and 39 weeks gestation. Imaging was performed using a General Electric 'Signa' 1.5T system using a fast-scan imaging technique already described (Garden *et al.* 1991).

Two women in the series had fetuses with gastroschisis; one had a diaphragmatic hernia; one had a twin pregnancy with both twins being affected by different renal abnormalities; one an abnormality confirmed at delivery to be micro-hydrancephaly; one fetus was hydropic with cystic lesions noted in the brain and one fetus had mild hydrops and cystic scalp lesions of undeterminate nature.

Imaging was performed with the mother lying in the right lateral position to prevent supine hypotension. Foam padding was used to maintain her position comfortably. Imaging was performed in a standard manner to obtain images in the maternal axial, sagittal and coronal planes. If necessary oblique images were then recorded to obtain standard views of the fetus. Echo delay time (TE), repetition times (TR), and flip angles were varied to achieve optimum fetal images. The commonest imaging sequence employed was TE 12 ms, TR 25 ms and flip angle of 10°. One image slice was produced in 3 s using this sequence.

Results

Patient 1

Generalized hydrops and cystic lesions in the cerebrum were seen when the patient was examined by ultrasound at 29 weeks gestation. F-SMRI failed to add information or assist in the diagnosis. The hydrops and the cystic lesions of the cerebrum could only be seen with difficulty.

Postmortem examination of this fetus showed

a male fetus with pleural effusions. Examination of the brain revealed friable fibrinous adhesions of the base of the brain and cystic softening of the cerebrum, possibly the result of intrauterine Coxsackie B virus infection.

Patient 2

The fetus was examined by ultrasound at 28 weeks gestation when scalp oedema and ascites were noted. Subsequent ultrasound examinations confirmed these findings and showed a cystic lesion on the scalp thought at one examination to be a cystic hygroma. Imaging by F-SMRI at 28 weeks gestation was again unhelpful; it was not possible to see the tissue oedema. A close examination of the scalp region did confirm the presence of a cystic lesion (Fig. 1) but no further information was available.

The woman was delivered preterm at 33 weeks gestation and the diagnosis of pulmonary lymphangiectasia was made. The lesions on the scalp were found on biopsy to be lymphangiomatosis (Thomas *et al.* 1990).

Patient 3

This patient had a twin pregnancy in which both twins were suspected of having different renal abnormalities. Ultrasound examination had shown twin 1 to have a right multicystic kidney; twin 2 was thought to have bilateral dysplastic kidneys and a hypoplastic left heart.



Fig. 1. Fetus at 30 weeks gestation with cystic area on scalp (indicated by arrow).

F-SMRI at 34 weeks gestation failed to demonstrate the bilateral dysplastic kidneys of the second twin. The diagnosis of a hypoplastic left heart could not be confirmed, the right multicystic kidney of the lower twin, however, could be clearly seen (Fig. 2). The maternal kidneys could also be seen and were found to be normal.

At birth, the presence of a right multicystic kidney in the first twin was confirmed by clinical examination and by ultrasound. DMSA scan revealed that the right kidney was non-functioning and that the left was slightly hypertrophied. The second twin was confirmed to have a hypoplastic left heart and died at 3 h of age. Post-mortem examination revealed dysplastic kidneys of Potter type IIa.

Patient 4

This woman had not attended for antenatal care until 28 weeks gestation, which ultrasound examination at that time had shown a fetus with a small head and hydrocephaly. These findings were also noted at a repeat examination 4 weeks later. F-SMRI at 32 weeks gestation showed no internal structures of the fetal brain (Fig. 3). Measurements of the depth of the frontal lobe and of the distance from the frontal to the occipital bone were markedly reduced.

Microcephaly was confirmed clinically in the newborn infant. Ultrasound and CT examinations suggested microcephaly and hydrancephaly with no cranial structures visible above the cerebellum. The infant died at 12 days. Post

mortem examination revealed a total brain weight of only 70 g.

Patients 5 and 6

Two patients had fetuses with gastroschisis and were imaged by F-SMRI at 35 and 38 weeks gestation, respectively. In both fetuses the abdomen, on sagittal section, was scaphoid in appearance. Bowel loops could be clearly seen in the amniotic fluid. By varying the settings used, particularly the flip angle, the loops of bowel could be seen more clearly (Fig. 4). In one of the fetuses, axial sections through the fetal abdomen showed an eccentric defect of between 1 and 2 cm in length (Fig. 5). This was confirmed following delivery.

Both infants did well after corrective surgery.

Patient 7

One fetus with a large left sided diaphragmatic hernia was imaged at 39 weeks gestation. The presence of the lesion was confirmed using F-SMRI, the bowel being seen to breach the diaphragm and displace the heart and lungs laterally. The size of the lungs was markedly reduced (Fig. 6). The patient was delivered the following day. Clinically the appearances at birth were those of diaphragmatic hernia. The child died a few hours after birth and post-mortem examination was refused.

The findings in these patients are summarized in Table 1.

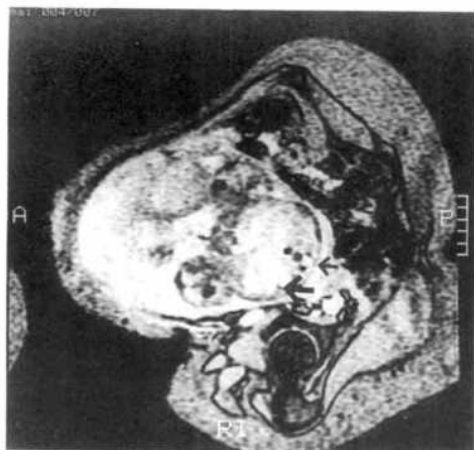


Fig. 2. Twin 1—Right multicystic kidney seen (fetal spine indicated by small arrow, right multicystic kidney by large arrow).

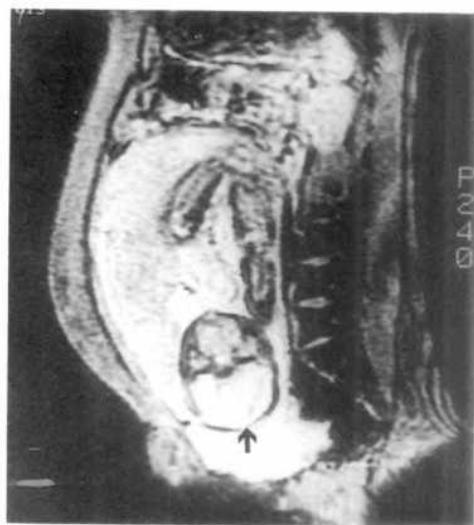


Fig. 3. No detail of fetal intracranial anatomy (arrow) seen in fetus with microhydrancephaly.

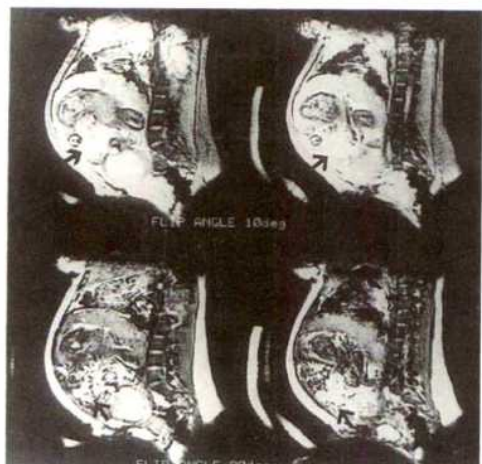


Fig. 4. Appearance of loops of bowel (indicated by arrows) in amniotic sac using different flip angles.

Discussion

Earlier work on the application of MRI in assessing fetal abnormalities have used conventional spin-echo imaging with consequent image distortion due to motion artefact. Consequently most of the reports have concerned single cases with no follow-up or assessment of the role of MRI.

From the present study it can be seen that the usefulness of MRI depends on the fetal abnormality. The abnormal accumulation of tissue fluid in hydrops or cystic subcutaneous structures was not well seen. McCarthy *et al.* (1985) imaged a fetus with cystic hygroma using conventional MRI scanning and commented on

their inability to see the lesion. They concluded that this was due to the similar relaxation behaviour of the amniotic fluid and the fluid in the cystic hygroma and limited spatial resolution preventing imaging of the membrane. The two pregnancies in this series were imaged at early gestations which probably contributed to the poor imaging due to limited spatial resolution. Other work still in progress in our unit suggests that, even using a fast scan imaging technique, MRI is of limited value before 34 weeks gestation.

MRI was unable to diagnose the presence of bilateral dysplastic kidneys in the second twin of patient 3, but the large right multicystic kidney was easily seen in the first twin. McCarthy *et al.* (1985) reported one fetus with urethral agenesis presenting with a distended bladder and left hydronephrosis on ultrasound imaging. This could be seen clearly on MRI, confirming the ultrasound diagnosis. The right kidney was dysplastic and that, too, could be seen in contrast to our experience. Weinreb *et al.* (1985), however, reported wrongly diagnosing, with MRI, a fetus who subsequently died of pulmonary hypoplasia and with features of Potter syndrome at birth as having bilateral hydronephrosis or cystic kidneys with sufficient renal function to produce urine.

The presence of a hypoplastic left heart in the second twin in our patient was not diagnosed by F-SMRI. The development of echoplanar imaging (Stehling *et al.* 1989) may overcome these problems but is not yet widely available. Only McCarthy *et al.* (1984) have reported being able

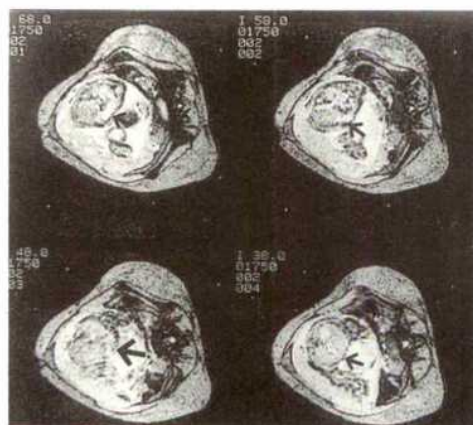


Fig. 5. Axial images of fetus with gastroschisis showing extent of lesion (small arrows indicate intact anterior abdominal wall, large arrow indicates defect).

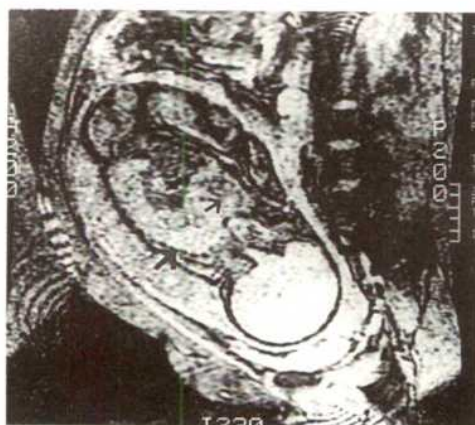


Fig. 6. Fetus with diaphragmatic hernia (large arrow) at 39 weeks gestation showing in thoracic cavity and lateral displacement of heart and lungs (small arrow).

Table 1.

Patient no	Gestation at MRI (weeks)	U/S findings	MRI findings	Pathology at birth
1	29	Hydrops, cerebral cystic lesions	Hydrops and cerebral cysts seen with difficulty	Pleural effusions, cystic softening of cerebrum (possible Coxsackie B infection)
2	28	Scalp oedema, ascites; cystic hygroma	Cystic scalp lesion	Pulmonary lymphangiectasia, lymphangiomata constricta
3	34	I Multicystic right kidney	Multicystic right kidney Maternal kidneys normal	Multicystic right kidney
		II Dysplastic kidneys, hypoplastic left heart	No abnormality seen	Potter type II Hypoplastic left heart
4	32	Microcephaly, hydrocephaly	Microcephaly, no brain tissue identified	Microcephaly, hydrancephaly, brain wt 70 g
5	35	Gastroschisis	Abdominal wall defect 1-2 cm	Gastroschisis 1-2 cm in length
6	38	Gastroschisis	Gastroschisis	Gastroschisis
7	39	Left diaphragmatic hernia	Left diaphragmatic hernia, pulmonary hypoplasia	Postmortem refused

to depict the fetal cardiovascular system by using MRI. They concluded that MRI did have potential as a second imaging technique after ultrasound but this has not been corroborated by other workers.

Several case reports have discussed the role of MRI in the diagnosis of fetal central nervous system abnormalities. Three were reported by McCarthy *et al.* (1985), two described ventriculomegaly in which the images obtained by MRI were better than those by ultrasound and the third fetus had an equivocal ultrasound examination from which they were not able to decide if the fetus had an abnormality of the posterior cranial fossa. MRI clearly depicted the contents of the posterior fossa as normal. Thickman *et al.* (1984) reported three fetal cerebral abnormalities imaged by both MRI and ultrasound. One had hydrocephalus, one had holoprosencephaly, and one diffuse brain oedema secondary to fetal death. In all three patients, MRI defined the intracranial structures well. Three patients in a series reported by Williamson *et al.* (1989) had intracranial abnormalities. One fetus had hydrocephaly; one had iniencephaly and one had an encephalocoele associated with Meckel-Gruber syndrome. As a conventional spin-echo imaging technique was used,

they had to abolish fetal movement by fetal neuromuscular blockade with pancuronium. They did, however, obtain particularly good MR images of the central nervous system and spinal cord. In the patient with Meckel-Gruber syndrome, the herniation of the brain contents into the sac could be seen by MRI. This could not be demonstrated by ultrasound due to the problem of oligohydramnios.

In our first patient the cystic lesions in the cerebrum could be seen only with difficulty. This patient was, however, imaged at an early gestation and this may be a contributory factor. The absence of any intracranial structures on post-mortem examination in patient 4 was in keeping with the MRI findings. The diagnosis of microcephaly was easily confirmed by MRI as the remainder of the facial skeleton could be easily assessed. The sloping forehead which is classically associated with microcephaly could also be clearly seen.

The soft-tissue gastrointestinal abnormalities of gastroschisis and diaphragmatic hernia were well demonstrated by MRI. In the two fetuses with gastroschisis, the abdominal wall profile in the sagittal plane was abnormal and loops of bowel could be seen in the defect in the axial sections of one of the fetuses. The information was

of benefit to the paediatric surgeons when counselling the pregnant woman before delivery. Measurements of soft tissue defects are difficult using ultrasound.

Stehling *et al.* (1989) also reported imaging a patient with gastroschisis using echo-planar MRI. They were able to image the gap in the abdominal wall and the prolapsed intestine. They also reported imaging a patient with diaphragmatic hernia. As most of these lesions are left sided, the prenatal diagnosis of diaphragmatic hernia using ultrasound usually depends on cardiac displacement to the right side of the chest cavity. Diagnosis of a right sided defect can be difficult because of the similar echogenicity of the liver and the lung on ultrasound. The appearances of liver, lung and bowel using MRI are very different and so should provide a useful adjunct to diagnosis. In addition, as in our last patient, the degree of pulmonary hypoplasia can be assessed which has an important bearing on prognosis.

We concluded that MRI has limited value in the diagnosis or further assessment of fetuses with abnormalities of tissue fluid. It is also of limited benefit in renal abnormalities unless the abnormality causes dilatation or cystic formation of the kidney. At present there is no role for F-SMRI in the diagnosis of fetal cardiovascular anomalies.

Our experience of central nervous system anomalies is too small to be certain about the role of MRI in their management. It may be that conventional spin-echo MRI will prove to be better than F-SMRI in these cases. The problem of image distortion due to fetal movement is not so marked in imaging the fetal brain as the head is relatively still compared to the rest of the fetal body. F-SMRI appeared to be most useful in the diagnosis and management of soft-tissue gastrointestinal abnormalities and provided information not available by ultrasound.

We would agree with Hill *et al.* (1988) that it is unlikely that MRI will replace ultrasound as the primary imaging technique in obstetrics, but it can provide extra information in defined situations.

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Fetal heart rate and intrauterine growth

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Abstract

Objective—To assess whether fetal heart rate in early and late pregnancy relates to size at birth.

Design—Prospective study of fetal heart rates in early and late pregnancy.

Setting—Princess Anne Hospital, Southampton.

Subjects—63 primigravid women.

Main outcome measures—Anthropometric measurements made on the newborn infant.

Results—There were no differences in heart rate between the sexes at 18 weeks gestation but by 36 weeks the boys had rates which were 4.4 beats lower than those of the girls. Higher fetal heart rate at 18 weeks was associated with lower ponderal index, smaller head circumference and smaller mid-arm circumference. There were no trends in fetal heart rate at 36 weeks with any birth measurements.

Conclusion—Babies born at term who have a pattern of neonatal measurements which reflect growth retardation have raised heart rates in early pregnancy. Influences which impair fetal growth appear to take effect early in gestation.

Recent studies have shown that patterns of fetal growth are strongly associated with blood pressure in adult life (Barker *et al.* 1989; 1990). In 449 men and women aged around 50 years blood pressure was inversely related to birthweight, but was positively associated with placental weight. Men and women who had had relatively low birthweight but heavy placental weight were at the highest risk of developing hypertension.

These trends were found in both sexes, and were independent of gestation and the main adult influences associated with blood pressure, body mass index and alcohol consumption. Further analyses of these data characterized two groups of babies, born at term, who developed high blood pressure as adults. The first were thin, having a below average birthweight, head circumference and placental weight. The second were short in relation to their head circumference, and had above average birthweight and placental weight (Barker *et al.* 1991).

The processes established prenatally which are associated with thinness at birth, or disproportionate head size and length, and which lead thereafter to high adult blood pressure, are unknown. One such process could be the intra-uterine 'setting' of heart rate, since pulse rate is known to relate positively to blood pressure both in children and in adults (Barker *et al.* 1989; Gillum 1988).

The aim of the present study was to investigate the changes in fetal heart rate occurring during gestation, and to relate these to birthweight, pla-

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cental weight and anthropometric measurements made on the infant at birth.

Subjects and methods

In total, 75 primigravid women agreed to take part in the study out of a series of 86 women approached whilst attending their first antenatal clinic at the Princess Anne Hospital, Southampton. All subjects were normotensive and without any relevant medical history. Their mean age was 24.7 (SD 4.5) years. Measurements of fetal heart rate were made in early pregnancy (15–21 weeks) and later pregnancy (34–39 weeks). Gestational age was determined from the date of the last menstrual period, and checked by a routine ultrasound scan made in early pregnancy; for nine women in whom these were discrepant by more than 2 weeks the scan value was used. Overall 70 women (93%) completed the study. Of the remaining five women, three had fetuses who died before 24 weeks gestation and two were delivered before a second determination of fetal heart rate was made. Two women were not included in the analysis because their placental weights were not recorded. Five women had pre-term deliveries (<37 weeks gestation) and were also excluded. We present therefore an analysis of 63 babies (31 boys and 32 girls). Complications occurred in five pregnancies (8%); these were mild pregnancy-induced hypertension in two, minor antepartum haemorrhage in two and anaemia in one. The value taken for the mothers' systolic blood pressure was their highest level recorded in the antenatal clinics during pregnancy. The study was approved by the local ethics committee.

Measurement of fetal heart rate

Fetal heart rate was measured using wide-beamed pulsed Doppler ultrasound (Hewlett Packard 8041A), over a 20–30 min period whilst the woman rested in a semi-recumbent position. The fetal heart rate record was divided into 5-min epochs and the average baseline heart rate was calculated for each epoch. The final heart rate was usually derived from the average of at least four epochs. However, problems were encountered in some of the early pregnancy recordings when contact with the fetal heart could be lost for several minutes as a result of fetal activity. In these fetuses the average of at least three 5-min epochs was used to derive the

heart rate. From 34 weeks gestation, heart rate was determined during periods of low heart rate variation (Wheeler & Murrills 1978; Visser *et al.* 1981). All heart rate recordings were analysed at the end of the study by the same observer (S.R.) and a sample of 95 traces was assessed independently by a second observer (T.W.). The mean difference between observers was 0.1 beats/min (SD 2.9). Analysis of variation in fetal heart rate in early pregnancy, determined in a sample of six babies studied on three occasions during the same week, showed a within subject standard deviation of 1.6 beats/min.

Anthropometric measurements

The measurements made on each infant were head (maximum occipito-frontal) circumference, chest and mid-arm circumferences, crown-heel length and subscapular skinfold thickness. All measurements were made three times, with the exception of subscapular skinfold thickness which was measured once. A mean of the three values was calculated. All measurements were made by one person (S.R.), 72% were made on the second day after delivery and all were made within 3 days.

Data analysis

Unpaired *t*-tests were used to compare means for the two sexes. Regression was used to examine relations between variables. An assessment of discordance between placental weight and birthweight was made by calculating the placental ratio (placental weight/birthweight). The fetal heart rate data from the 70 subjects who completed the study, including 36 additional measurements obtained between 28 and 34 weeks, were analysed using the LMS method of Cole (1988). Standard normal scores for fetal heart rates in early (15–21 weeks) or late (34–39 weeks) pregnancy were derived. These scores were transformed to become standardized heart rates at 18.0 or 36.0 weeks, permitting direct comparison between individuals regardless of the exact date of their measurement.

Results

Fig. 1 shows the values of fetal heart rate for the 63 babies. Fetal heart rate fell with advancing gestation whilst the spread in values among the babies increased. The rate of fall in fetal heart

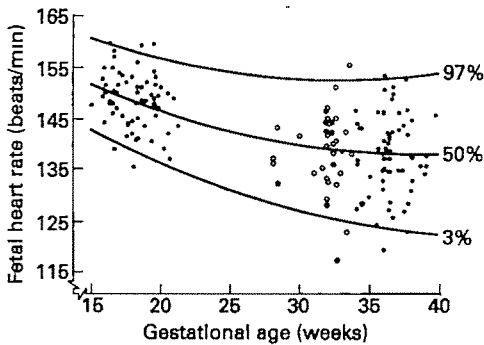


Fig 1. Fetal heart rates recorded from 63 subjects during early ($\bullet$, $n = 63$), mid ($\circ$; $n = 35$) and late ($\bullet$; $n = 63$) gestation. Centiles derived from 70 subjects (see Subjects and methods).

rate changed over the course of gestation, being greatest in early pregnancy (15–21 weeks) and slowing in later pregnancy (34–39 weeks).

The mean values of fetal heart rate, standardized as described, are given in Table 1. At 18 weeks, values for the two sexes were similar, but by 36 weeks a statistically significant difference had emerged with boys having heart rates 4.4 beats/min lower than those of the girls (95% CI 0.8–8.0, $P = 0.02$). The two sexes were of similar size at birth. Using a test at the 5% level, there were no statistically significant differences in average weight, length, head, chest and mid-arm circumferences nor in placental weight or placental ratio. The girls were, however, fatter than the boys, having greater mean subscapular skinfold thickness, 5.1 mm compared with 4.5 mm (difference 0.7 mm, 95% CI 0.2–1.2, $P = 0.01$), and a higher mean ponderal index 2.79 compared with 2.67 (difference 0.12, 95% CI 0.01–0.23, $P = 0.03$).

Mean values of birth measurements and maternal blood pressure are given in Table 2. Higher heart rate at 18 weeks gestation was asso-

ciated with lower birthweight and smaller head circumference but there was no association with length. Lower fetal heart rates at 18 weeks tended to be associated with a longer gestation though this was not statistically significant. Allowance for duration of pregnancy reduced, but did not abolish, the associations of heart rate with birthweight and head circumference. Higher fetal heart rate at 18 weeks was associated with a lower ponderal index at birth, an association which was independent of duration of pregnancy. Heart rate was also inversely related to mid-arm circumference. It was not related to placental weight, placental ratio, maximum maternal systolic pressure, subscapular skinfold thickness or chest circumference. The slope and 95% CI for the association between each birth measurement and fetal heart rate at 36 weeks are also given in Table 2. Heart rate at 36 weeks was not related to any birth measurement nor to the maternal blood pressure.

Table 3 shows that there was statistically significant associations between ponderal index and head circumference ($P = 0.0003$), mid-arm circumference ($P < 0.0001$) and subscapular skinfold thickness ($P = 0.0004$).

Although maternal systolic pressure was not related to fetal heart rate at 18 or 36 weeks (Table 2) the magnitude of the fall in heart rate over the period was inversely related to the maternal blood pressure. This relation was not, however, statistically significant ($P = 0.08$). The smallest falls in heart rate were found in babies of mothers whose maximum systolic blood pressure was above 130 mm Hg, the fall being 8.4 beats/min compared with 12.3 beats/min in the babies whose mothers had a maximum blood pressure of ≤ 120 mm Hg. There were no significant differences in heart rate between the babies of mothers who smoked during pregnancy ($n = 15$) and those who did not smoke ($n = 48$).

Table 1. Mean fetal heart rates (beats/min) in early and late gestation

Gestation (weeks)	Fetal heart rate (beats/min)	
	Boys ($n = 31$)	Girls ($n = 32$)
18	148.5 (6.1)	148.7 (4.4)
36	135.7* (8.8)	140.1 (5.3)

Figures in parentheses are standard deviations

* $P = 0.02$ boys vs girls

Discussion

We have examined fetal heart rates at 18 and 36 weeks in 63 primigravid women whose babies were born at term. The fall in basal fetal heart rate with advancing gestation which we found accords with the findings of other studies (Dawson *et al.* 1985; Ibarra-Polo *et al.* 1972). Our data confirm those of Wheeler & Murrills (1978) who showed a slowing in the rate of fall together with

Table 2. Regressions of birth measurements and maternal blood pressure with fetal heart rate at 18 and 36 weeks

Dependent variable	Mean (SD)	18 weeks			36 weeks		
		Slope per beat	95% CI	P	Slope per beat	95% CI	P
Birthweight (g)	3469 (407)	-22.0	-40.9 to -3.1	0.02	-0.65	-15.1 to 13.8	0.93
Head circumference (cm)	35.0 (1.3)	-0.08	-0.14 to -0.02	0.01	-0.03	-0.07 to 0.02	0.27
Length (cm)	50.3 (1.8)	-0.02	-0.11 to 0.07	0.63	0.01	-0.05 to 0.08	0.75
Gestation (weeks)	40.2 (1.3)	-0.05	-0.12 to 0.01	0.09	0.00	-0.05 to 0.05	0.95
Ponderal index (g/cm ³ × 100)	2.73 (0.23)	-0.01	-0.02 to 0.00	0.01	0.00	-0.01 to 0.01	0.49
Mid-arm circumference (cm)	10.9 (0.8)	-0.04	-0.08 to 0.00	0.05	0.01	-0.02 to 0.04	0.60
Placental weight (g)	647 (111)	-0.63	-6.05 to 4.80	0.82	-1.29	-5.26 to 2.68	0.52
Maximum maternal systolic blood pressure (mmHg)	126.5 (9.9)	-0.24	-0.70 to 0.22	0.30	0.16	-0.18 to 0.49	0.36

an increasing between-fetus variability among the values in late pregnancy.

To our knowledge a difference in fetal heart rate between the sexes at 36 weeks has not been found in other studies. It is possible that by calculating a 'standardized' 36-week value which takes into account the important effect of gestational age upon heart rate, we have been able to show a difference which has been obscured in studies where this has not been done. The difference between the sexes was not explained by size at birth. A higher pulse rate of 3 beats/min in girls over boys at the age of 10 years has been recorded (Barker *et al.* 1989) and similarly was not explained by a difference in height.

We found that babies who had a lower birthweight, a smaller head circumference at birth and who were thin, having a low ponderal index, had higher heart rates at 18 weeks gestation. The association with lower birthweight and head circumference partly resulted from earlier birth in babies with higher heart rates. The remainder of the association may therefore be due to retarded growth. The association of heart rate with ponderal index was independent of gestation. We found no associations between birth

measurements and fetal heart rate at 36 weeks gestation. This could be due to the small number of individuals studied at a time of increasing inter-individual variability amongst the values. However, Gagnon *et al.* (1989) report that basal fetal heart rates in a group of small-for-gestational-age fetuses between 30 and 40 weeks gestation were similar to those in a group exhibiting normal growth.

Since the association of lower birthweight and head size with faster heart rate at 18 weeks partly depended on retarded fetal growth rather than shorter gestation, it is possible that the faster heart rates resulted from the babies already being small in mid-gestation. Alternatively the faster heart rate could be an early adaptive response to adverse influences which later cause both growth failure and early delivery. Whatever the explanation, our results show that term babies with low ponderal indices, small heads, thin arms and less subcutaneous fat (Table 3) already differ from other babies in early gestation. A study of men and women aged 50 years has shown that such babies have high adult blood pressure (Barker *et al.* 1990). A study of 4-year old children similarly showed that they had

Table 3. Head and mid-arm circumference, and subscapular skinfold thickness in relation to thirds of ponderal index

Thurds of ponderal index (g/cm ³ × 100)	Head circumference (cm)	Mid-arm circumference (cm)	Subscapular skinfold thickness (mm)
<2.62	34.4 (1.3)	10.4 (0.8)	4.2 (0.8)
2.62-2.81	34.9 (1.4)	10.9 (0.8)	4.8 (1.0)
≥2.81	35.6 (0.9)	11.3 (0.7)	5.4 (1.2)

Figures in parentheses are standard deviations.

higher systolic blood pressure (Law *et al.* 1991). Our findings suggest that these babies would have had raised heart rates in early gestation.

Maternal blood pressure was not related to fetal heart rate at 18 or 36 weeks (Table 2). We found, however, that when the highest maternal systolic pressure in pregnancy was >130 mm Hg, the fall in fetal heart rate during gestation was less. This is consistent with the findings of Dawson *et al.* (1985) who demonstrated reduced falls in fetal heart rate in the babies of six women who became hypertensive compared with controls. We found no effect of maternal smoking habits on fetal heart rate.

In conclusion we have shown that babies born at term with low ponderal indices and small head and mid-arm circumferences have raised heart rates in early pregnancy. This pattern of neonatal measurements, which reflects impaired fetal growth, has been shown to predict high blood pressure in adult life. Intrauterine 'setting' of heart rate may be one mechanism linking impaired fetal growth with later high blood pressure. The influences which impair growth appear to take effect early in gestation and are at present unknown.

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Chromosome abnormalities detected in chorionic villus biopsies of failing pregnancies in a subfertile population

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Abstract

Objective—To determine the range and prevalence of chromosomal abnormalities occurring in failing pregnancies in subfertile women.

Design—Prospective biochemical and ultrasound monitoring of all pregnancies conceived between 1988 and 1990 in a subfertile population.

Setting—A single-centre specialist fertility clinic in Perth, Western Australia.

Subjects—Tissue from 50 early pregnancy losses was successfully cultured for chromosomal analysis from 46 pregnancies comprising 29 anembryonic pregnancies, 9 miscarriages and 8 ectopic pregnancies.

Main outcome measures—Impending pregnancy loss was identified at an early stage. Chromosomal analysis was performed on chorionic villi obtained before the diagnosis became clinically evident.

Results—Significant chromosomal abnormalities were identified in 54% (14/26) of early pregnancy losses where gamete manipulation was involved and 45% (9/20) of those following spontaneous conception. The most common abnormalities were trisomies (12 pregnancies, mainly trisomy 16), triploidies (3 pregnancies) and monosomy X (3 pregnancies). An excess of female fetuses was noted with only 24% of conceptuses (11/46) bearing a Y chromosome.

Conclusions—The data indicate a similar rate of chromosomal abnormalities underlying pregnancy losses at earlier stages of pregnancy and after infertility treatments as that reported from the general population. Gamete manipulation does not appear to confer a higher rate of chromosomal abnormalities in ensuing pregnancies.

The diagnosis of pregnancy in women who conceive after subfertility should be received with

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cautious optimism as early pregnancy wastage is high (25–30%) and includes a 5–6% risk of ectopic pregnancy (Yovich & Matson 1988; National Perinatal Statistics Unit 1990). The underlying causes of pregnancy wastage are likely to be related to the same factors responsible for implantation disorders, namely embryo quality and uterine receptivity (Yovich & Lower 1990). A major contribution to embryo abnormality undoubtedly arises from underlying chromosomal defects. Previous studies have identified chromosome abnormalities in approximately 50% of the products of conception which were karyotyped after miscarriage (Boue *et al.* 1975; Hassold *et al.* 1980b; Byrne *et al.* 1985). These

studies were performed in the general population and examined the products of conception after the diagnosis had been made on clinical grounds, in most cases after miscarriage had occurred. Since there is a high rate of pregnancy wastage in women who conceive after assisted conception, monitoring of serum hormone estimations and serial ultrasound examination is offered to women at PIVET Medical Centre during the first trimester. This has enabled failing pregnancies to be identified before the diagnosis becomes clinically obvious (Yovich *et al.* 1986). Chorionic villus samples have thus been obtained at an earlier stage of gestation providing a prospective study of all failing pregnancies which occurred in a subfertile population from a single centre.

Subjects and methods

Subfertile women conceiving at PIVET Medical Centre as a result of assisted conception procedures, artificial insemination or timed intercourse were monitored through the luteal phase and the first trimester by serial estimations of serum levels of the β -subunit of human chorionic gonadotrophin (β -hCG), oestradiol and progesterone, with ultrasound examination at 7 weeks gestation (dated from the last menstrual period (LMP) or adjusted LMP) or earlier if indicated. Early pregnancy losses were diagnosed according to the following criteria.

Blighted ovum (Anembryonic pregnancy)

In 30 women early ultrasound examination revealed an empty intrauterine gestation sac associated with static or falling serum β -hCG levels. Mean gestational age at sampling was 7.72 weeks (range 7–10 weeks).

Spontaneous fetal death (miscarriage)

Eleven women had a diagnosis of absent fetal heart activity and failure in growth of the gestation sac, when positive fetal heart activity had previously been diagnosed at ultrasound scan. Mean gestational age at sampling was 10.5 weeks (range 8–17 weeks).

Ectopic pregnancy

This was strongly suspected in nine women when ultrasound examination failed to confirm the

presence of an intrauterine gestation sac in association with raised serum β -hCG. The diagnosis was confirmed at laparoscopy or laparotomy. Mean gestational age at sampling was 7.44 weeks (range 6–8 weeks).

Chorionic villus sampling

Chorionic villi were obtained at the time of but before surgical termination of pregnancy using a malleable Birmingham transcervical aluminium catheter (Rocket, London). Specimens were immediately examined in the adjacent IVF laboratory at $\times 40$ magnification using an inverted microscope. Villi were dissected free from any contaminating maternal blood and tissue by the embryologist before being placed in a Tyrodes based solution with Hepes buffer (Quinn *et al.* 1985) and transported to the cytogenetics laboratory. There the specimen was again inspected using an inverted microscope and pieces of villi were selected for culture. These were washed several times in phosphate buffered saline and dissected free of all maternal tissue. When readily identifiable villi could not be separated, a portion of membranous tissue was selected and cleaned but the specimen was classified as products of conception rather than confirmed villi.

The specimen was then minced and cultured in Chang's medium in 5% CO₂ at 37°C. When cultures were confluent they were trypsinized and harvested subsequently by the suspension method after exposure to Colcemid for approximately 3 h, followed by hypotonic treatment and fixation in 3:1 methanol/acetic acid. A minimum of 15 cells were analyzed from each specimen. Identification of chromosomes was made using GTG banding (Seabright 1971) (Fig. 1).

Results

Over a 2-year period 50 pregnancies were examined. Four have been excluded because of failed culture. Of the remaining 46 pregnancies there were 29 blighted ova, 9 miscarriages and 8 ectopic pregnancies. In 10 of the 29 blighted ovum pregnancies and in 1 of the 9 miscarriages readily identifiable villi could not be unequivocally separated and the culture specimen, consisting of membranous tissue, was classified as products of conception. These 11 specimens all gave normal 46XX karyotypes. Whilst most of these karyotypes are thought to be of fetal origin, it

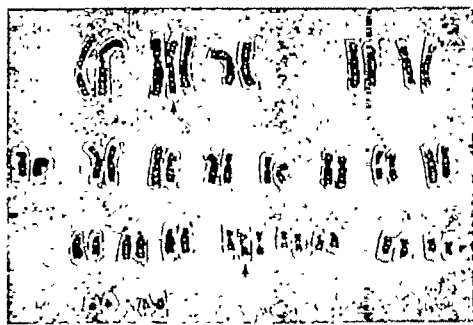


Fig. 1. Human karyotype obtained using GTG banding. 48XX+2+16.

was not possible to confirm conclusively that some were not of maternal origin.

Table 1 summarises the number and types of chromosomal abnormalities obtained in conceptions with respect to gamete manipulation. The proportion of abnormalities in early pregnancy losses following gamete manipulation (14/26; 54%) is not significantly different from those following natural conception (9/20; 45%). The results are presented graphically in Fig. 2. Anembryonic pregnancies and miscarriages revealed a higher proportion of chromosomal abnormalities than ectopic pregnancies.

There was no statistically significant difference in the maternal age between the women who experienced an early pregnancy loss with a normal karyotype and those with an abnormal karyotype (mean age 32.2 years, SD 4.3 vs mean 32.8 years, SD 4.7).

Discussion

As the laboratory techniques associated with assisted conception have improved, and particularly with the introduction of new procedures for the treatment of male infertility, the fertilization rate of oocytes following IVF has risen to around 80%. This compares favourably with an estimation of 84% of human ova exposed to the opportunity of fertilization *in vivo* (Leridon 1977). However, the clinical pregnancy rate is still relatively low, diminished in part by failure to implant and partly from preclinical losses (Yovich & Matson 1988). Chromosomal abnormalities have been demonstrated in 40% of preimplantation embryos generated following IVF (Papadopoulos *et al.* 1989) and have been shown to be by far the most common identifiable defect among early pregnancy losses occurring after implantation. One might speculate that

other aetiological factors peculiar to pregnancies conceived following IVF could have an adverse effect on the rate of early pregnancy loss. Our results do not confirm this, with approximately 50% being affected by chromosomal abnormalities. Furthermore in a study conducted by postal questionnaire of more than 200 European IVF centres, 21 of 34 (62%) fetal losses karyotyped demonstrated a chromosomal abnormality (Plachot 1989). One small study from a single assisted conception unit reported 5 abnormalities out of 13 successfully karyotyped miscarried fetuses (Roesler *et al.* 1989). Other studies, not confined to the subfertile populations, also encountered abnormalities in around 50% of lost fetuses (Boue *et al.* 1975). Data pooled from several series reveals an overall prevalence of chromosomal abnormality in 46% of miscarriages recognized in the first trimester (Simpson & Bombard 1987). The most common anomaly was autosomal trisomy accounting for 50% of all abnormalities detected and 22% of all miscarriages for which karyotypes were available. A more recent study has demonstrated an even higher proportion of abnormalities (76.7%) although a number of these women had been referred for chorionic villus sampling because of increased risk of fetal chromosomal abnormality (Gueneri *et al.* 1987).

The relation between maternal age and aneuploidy is well established, in particular for trisomy 21 (Penrose, 1933). Our findings were not influenced by age-related effects since no significant difference was noted in maternal age between women losing normal and abnormal conceptuses.

Our findings indicate a male karyotype is less likely to miscarry. There was not a single normal

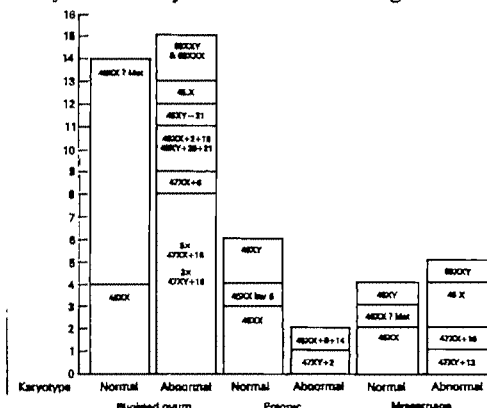


Fig. 2. Distribution and types of chromosomal abnormalities.

Table 1. Karyotyping of early pregnancy losses in 46 subfertile women

Subject No.	Age (years)	Stimulation protocol	Procedure	Diagnosis	Tissue examined	Karyotype
Gamete manipulation						
1	40	Lucrin/hMG	IVF-ET	Bl ovum	Conf villi	47XX+16
30	37	Lucrin/hMG	IVF-ET	Ectopic	Conf villi	47XY+20
24	32	Lucrin/hMG	IVF-ET	Bl ovum	POC	46XX
2	26	Lucrin/hMG	PROST	Bl ovum	Conf villi	48XX+2+16
38	31	Lucrin/hMG	PROST	Miscarriage	Conf villi	45,X
3	36	Lucrin/hMG	TEST	Bl ovum	Conf villi	47XX+16 inv 2
4	29	Lucrin/hMG	TEST	Bl ovum	Conf villi	45XY-21
31	38	Lucrin/hMG	TEST	Ectopic	Conf villi	48XX+8+14
40	34	Lucrin/hMG	TEST	Miscarriage	Conf villi	47XY+13
16	32	Lucrin/hMG	TEST	Bl ovum	Conf villi	46XX
20	33	Lucrin/hMG	TEST	Bl ovum	POC	46XX
21	38	Lucrin/hMG	TEST	Bl ovum	POC	46XX
22	38	Lucrin/hMG	TEST	Bl ovum	POC	46XX
19	29	hCG	FROST	Bl ovum	Conf villi	46XX
7	33	Nil	FET	Bl ovum	Conf villi	47XY+16
34	34	Nil	FET	Ectopic	Conf villi	46XY
41	38	Lucrin/hMG	GIFT	Miscarriage	Conf villi	47XX+15
39	30	Lucrin/hMG	GIFT	Miscarriage	Conf villi	45,X
32	33	Lucrin/hMG	GIFT	Ectopic	Conf villi	46XX inv 6
23	41	Lucrin/hMG	GIFT	Bl ovum	POC	46XX
45	41	HRT	ET OD	Miscarriage	Conf villi	46XX
5	34	hMG	DI	Bl ovum	Conf villi	47XX+16
6	41	hMG	i/c	Bl ovum	Conf villi	48XY+20+21
46	30	hMG	i/c	Miscarriage	POC	46XX
17	28	CC/hMG	i/c	Bl ovum	Conf villi	46XX
18	29	CC	i/c	Bl ovum	Conf villi	46XX (Twins)
Natural conception						
9	26	Nil	i/c	Bl ovum	Conf villi	47XX+16
10	37	Nil	i/c	Bl ovum	Conf villi	47XX+16
11	30	Nil	i/c	Bl ovum	Conf villi	47XY+16
13	38	Nil	i/c	Bl ovum	Conf villi	47XY+16
14	31	Nil	i/c	Bl ovum	Conf villi	47XX+6
8	27	Nil	i/c	Bl ovum	Conf villi	69XXY
12	31	Nil	i/c	Bl ovum	Conf villi	69XXX
42	31	Nil	i/c	Miscarriage	Conf villi	69XXY
15	24	Nil	i/c	Bl ovum	Conf villi	45,X
33	29	Nil	i/c	Ectopic	Conf villi	46XY
44	37	Nil	i/c	Miscarriage	Conf villi	46XY
35	27	Nil	i/c	Ectopic	Conf villi	46XX
36	33	Nil	i/c	Ectopic	Conf villi	46XX
37	31	Nil	i/c	Ectopic	Conf villi	46XX
43	27	Nil	i/c	Miscarriage	Conf villi	46XX
25	31	Nil	i/c	Bl ovum	POC	46XX
26	35	Nil	i/c	Bl ovum	POC	46XX
27	27	Nil	i/c	Bl ovum	POC	46XX
28	28	Nil	i/c	Bl ovum	POC	46XX
29	31	Nil	i/c	Bl ovum	POC	46XX

Abbreviations. Lucrin = Leuprolide Acetate (GnRH Analog); hMG = human menopausal gonadotrophin, HRT = hormone replacement therapy; CC = clomiphene citrate; IVF-ET = in vitro fertilization and embryo transfer, PROST = pronuclear stage tubal transfer; TEST = tubal embryo stage transfer; FROST = frozen/thawed embryo salpingeal transfer, FET = frozen embryo transfer; GIFT = gamete intrafallopian transfer; ET OD = intrauterine embryo transfer donated oocyte, DI = Donor insemination; i/c = timed/natural intercourse; Conf villi = confirmed villi on culture; POC = culture of villi not confirmed.

male karyotype among the blighted ovum pregnancies which constitute the major proportion of all pregnancy failures. Furthermore, only 24% of all conceptuses karyotyped bore a Y chromosome, and only 13% of the conceptuses with apparently normal karyotypes were male. Even if the 11 pregnancies in which definite villi were not identified are excluded, only 25% of normals were male. Data from the National Perinatal Statistics Unit in Australia and New Zealand where the overall sex ratio in singleton births following IVF procedures in 1988 was 1.03 has confirmed that gamete manipulation cannot be held responsible for such variation between the sexes (National Perinatal Statistics Unit 1990). An excess of female miscarried fetuses over males was also noted in the two largest reported series of miscarriages (Boue *et al.* 1975; Creasy *et al.* 1976). A more recent report from Germany of 750 miscarriages also demonstrated an excess of female karyotypes in chromosomally normal fetuses (male : female ratio 0.71) (Eiben *et al.* 1990). Since it has already been acknowledged that the sex ratio approaches unity at birth, the data suggest that more female embryos must either fertilize or implant.

Knowledge of the karyotype may be of relevance to the prognosis in subsequent pregnancies. An abnormal chromosome complement was found in 80% of pregnancies in women whose previous pregnancy resulted in miscarriage with chromosomal abnormalities (Hassold 1980a). In other words certain couples seem to be predisposed to recurrent aneuploidy. Whilst this is often manifest as recurrent miscarriage, several studies have indicated that the risk of liveborn trisomy 21 following miscarriage of a trisomic pregnancy is about 1% (Alberman 1981). Therefore consideration should be given to prenatal diagnosis in such women.

Two of the three triploid karyotypes identified are of particular interest as they occurred in consecutive naturally conceived pregnancies in the same woman. Whether these lesions were the result of polyspermic fertilization or caused by a defect of cell division is unknown. Controlled IVF is proposed as a diagnostic test for this couple. If polyspermic fertilization is demonstrated at the pronuclear stage then the condition may be amenable to specific treatment by microinjection of a single spermatozoon if the technique of micromanipulation continues to develop from its present stage (Ng *et al.* 1988). The importance of careful examination of the

fertilised oocytes at the pronuclear stage has been stressed previously (Yovich, 1985). In particular this will allow oocytes with odd numbers of pronuclei to be discarded. There were no cases of polyploidy amongst those pregnancies conceived following IVF in the present series.

In summary, early diagnosis of pregnancy failure has enabled accurate karyotyping in a high proportion of the early pregnancy losses arising after treatment in this clinic. The results are largely in agreement with the published series of chromosomal analysis of the products of conception obtained following miscarriage in the fertile population; a similar range and distribution of karyotypes were obtained.

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Emergency cervical cerclage

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Abstract

Objective—To assess the efficacy of emergency cervical cerclage.

Design—Retrospective review of patients who underwent emergency cervical cerclage between August 1986 and August 1989.

Setting—University College and the Middlesex Hospitals obstetric unit, a neonatal referral centre.

Subjects—19 women between 16 and 28 weeks gestation with a cervical dilatation between 3 and 10 cm. There were two twin pregnancies.

Interventions—Amniocentesis and bacteriological assessments were performed prior to cerclage and prophylactic antibiotics were given. Insertion of sutures was aided by a combination of techniques described previously.

Main outcome measures—Prolongation of gestation and pregnancy outcome. Bacteriological findings at delivery and maternal and fetal morbidity were also recorded.

Results—Membranes remained intact in all the women after cerclage. Fifteen live babies were born and 13 of them survived (survival rate 63%). Gestation was prolonged from between 1 and 19 weeks in these patients and the gestational age at delivery ranged from 25 to 41 weeks. All eight intrauterine or neonatal deaths were associated with infection. Infecting organisms included *Escherichia coli*, *Gardnerella vaginalis*, *Mycoplasma hominis*, *Trichomonas vaginalis* and *Fusobacterium* spp. Pregnancy was prolonged for ≤ 5 weeks in these infected pregnancies. A cervical laceration occurred in a patient who had the suture inserted at full dilatation and subsequently laboured, but there were no other maternal complications.

Conclusions—Emergency cervical cerclage can prolong pregnancy and influence the outcome favourably.

Cervical cerclage was first described by Shirodkar (1960) at the French Society of Gynaecology in Paris in 1951. McDonald (1957) had also used cerclage and described his first series of 70 women. Since then the technique has been used both electively and, after cervical dilatation has occurred, as an emergency procedure. There has been concern that elective cerclage was over-used and its efficacy is at present the subject of a joint trial (MRC/ROG Working Party on Cervi-

cal Cerclage 1988). Emergency cerclage is less commonly performed, but McDonald (1957), Harger (1980) and Kuhn & Pepperell (1977) reported success rates of 43%, 59% and 60% respectively. In another study, fetal survival was 80% with cerclage at a cervical dilatation of < 5 cm, but only 24% when cervical dilatation was ≥ 5 cm (Forster 1967). Women without a history of cervical incompetence may present at an early gestational age with a dilated and sometimes even a fully dilated cervix. The reasons for this are multiple (Cousins 1980) but it is clear that such a situation is not always unsalvageable. Previous studies suggest that intervention can prolong the pregnancy to viability but also report difficulty with membrane rupture during the procedure, or infection, resulting in preg-

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nancy loss (Harger 1980; Kuhn & Pepperell 1977).

We have attempted to improve the results of emergency cervical cerclage by excluding patients with evidence of infective aetiology, by improving operative techniques so that the membranes do not rupture during the procedure, and by using prophylactic antibiotics to prevent postoperative infection.

Patients and methods

Nineteen patients underwent emergency cerclage at University College and Middlesex Hospitals, London, between August 1986 and August 1989. Their details are shown in Table 1. Gestational age at the time of insertion of the suture ranged from 16 to 28 weeks and the cervical dilatation was between 3 and 10 cm. In eight women the cervix was ≥ 5 cm dilated at the time of the procedure. The cervix was effaced in all patients.

Infection was excluded clinically (by absence of pyrexia and uterine tenderness) and by microbiological assessment. Seventeen of the women had an amniocentesis in addition to high vaginal and cervical swabs and blood cultures. A sample of amniotic fluid was treated with Gram's stain and examined under the microscope, further samples were cultured under aerobic and anaerobic conditions. Two patients had positive cultures. *Gardnerella vaginalis* was cultured from amniotic fluid obtained from patient no. 7, but after treatment with metronidazole a second amniocentesis provided a negative sample. A slow growing species of *Fusobacterium* was identified in the amniotic fluid obtained from patient no. 17, 7 days after suture insertion. Patients nos. 1 and 16 did not have an amniocentesis and no fluid was obtained in patient 18. High vaginal swabs were examined microscopically for *Trichomonas vaginalis* and then cultured for bacteria and *Candida* spp. Cervical swabs were examined for *Chlamydia trachomatis* (ELISA) and cultured for bacteria and *Mycoplasma* spp. Eighteen patients in this series had high vaginal and cervical swabs taken prior to cerclage and these were negative (normal flora only) in all patients. No swabs were obtained from patient 18. Blood cultures were all negative. C-reactive protein estimation was used to screen patients postoperatively for evidence of infection.

Most of the patients were observed for 8–12 h before insertion of the suture to ensure that the

cervical dilatation was not the result of an active attempt by the uterus to expel its contents. Women with persisting contractions, those who had evidence of infection and those who had a recent history of antepartum haemorrhage suggestive of placental abruption were excluded.

Patients selected for cerclage were given prophylactic tocolysis, using either an intravenous infusion of ritodrine (50 µg in 500 ml 0.9% saline at an initial infusion rate of 5 drops per min) or indomethacin 100 mg rectally twice daily, or both. Under general anaesthesia they were placed in lithotomy position with steep Trendelenburg tilt, and the situation was assessed by cautious insertion of a Sim's speculum. If the cervix was identifiable and the membranes were not protruding down the vagina in an hour-glass formation, an attempt was made to push the membranes up into the uterus with an inflated Foley catheter, as described previously by Sher (1979) and Holman (1973). The technique involves grasping the edge of the cervix with sponge holding forceps, drawing the cervix down and then carefully placing the Foley catheter against the membranes. The membranes are not touched with sponges, gauze or any instruments. Gentle pressure is used to replace the membranes. The Foley catheter balloon can be inflated or deflated to enable it to fit into the available space and when the membranes have been replaced, 30–50 ml of water is left in the balloon to hold the membranes up and out of the way. This allows insertion of sutures without risk of putting a needle through the amniotic sac. If the membranes were bulging through the cervix in an hour-glass formation, reduction was not always achieved with Trendelenburg tilt, tocolysis and pressure. These patients had an ultrasound directed amniocentesis, as described by Goodlin (1979), and sufficient amniotic fluid was withdrawn (200–300 ml in most patients) to enable replacement of the membranes.

The first six patients in the series and patients 9 and 12 had a Mersilene tape (Ethicon Ltd.) suture inserted using the McDonald (1957) technique. It was our impression that this was likely to be associated with postoperative infective complications and we therefore adopted a technique using interrupted nylon or prolene sutures (0 metric gauge) placed between the anterior and posterior surface of the cervix as in the Wurm procedure (Hefner *et al.* 1961). The number of sutures varied but generally five or six were used to close the cervix from as near to the

Table 1. Emergency cervical cerclage results

Patient no	Age (years)	Gestational age at cerclage (weeks + days)	Cervical dilatation (cm)	Prolongation of pregnancy (weeks)	Bacteriology at delivery	Birthweight (g)	Gestation at delivery (weeks)	Outcome
1	32	1+6	8	12	No infection	2108	32	Survived
2	31	23	3	2	AF -ve, placenta, urine, blood, suture <i>E. coli</i>	650	25	NND at 5 days broncho-pneumonia
3	20	27	3	5	CS: mixed anaerobes, HVS: anaerobic strep AF <i>Bacteroides</i> spp	2312	32	Survived
4	26	23+6	4	17	No infection	4000	41	Survived
5	40	17	3	19	No infection	2350	36	Survived
6	24	19	4	6	HVS <i>E. coli</i>	722	25	Survived
7	31	24+3	8	1	Chorioamnionitis, PS:-vt	680	25	IUD, pneumonia
8	35	25+2	4	3+5	No infection	1294	29	Survived
9	31	22	4	3	Chorioamnionitis PS: <i>M. hominis</i>	1283	29	Survived
10	30	22	4	0+3	HVS/CS <i>Trichomonas</i> , <i>M. hominis</i> and mixed anaerobes, PS -ve, no chorioamnionitis	572 900	25 22	Twin 1 miscarried before cerclage NND (Twin 2) IUD
11	31	21+2	4	8	No infection	1394	29	Survived
12	33	28	3	4	No infection	1966	32	Survived
13	36	19+5	5	7	PS, <i>E. coli</i>	1065	27	Survived
14	31	20	5	5	Chorioamnionitis, swabs. -ve	800	25	IUD
15	37	21	8	4	PS mixed anaerobes, MSU, <i>E. coli</i> . Elevated CRP	769	25	Survived
16	31	27	3	11	No infection	3700	38	Survived
17	32	16	8	1+4	CS, mixed anaerobes chorioamnionitis	—	17	IUD
18	19	20	10	0+1	No bacteriology, no AF	—	20	IUD, cervical tear
19	29	25	5	1+	HVS: mixed anaerobes	826	26	Survived

Abbreviations AF = amniotic fluid; IUD = intrauterine death; CS = cervical swab, HVS = high vaginal swab; PS = placental swab; MSU = midstream urine specimen, CRP = C-reactive protein

internal os as possible down to the external os. The sutures were tied to bring the anterior and posterior surfaces of the cervix together, without occluding the circulation.

Tocolysis was continued for 6 to 12 h post-operatively and the patients were observed on the labour ward. Prophylactic antibiotics were given intravenously during the procedure to 14 patients and continued for 48 h (patients 1-3, 7-9 and 12-19). Most patients received clindamycin with or without gentamicin, and one patient was given cefuroxime (no. 1). The combination of clindamycin and gentamicin was used because

these antibiotics cover a broad range of aerobic and anaerobic bacteria, *M. hominis* and *C. trachomatis*. If the procedure was successful and no complications ensued, patients were usually discharged a week after cerclage with instructions to lead a quiet life, avoid intercourse and attend the antenatal clinic for assessment at 2 week intervals.

Results

There were 17 singleton and two twin pregnancies (Table 1). The operative procedure was

technically successful in all patients in that the membranes remained intact during the procedure. Fifteen live babies were born and 12 of them survived. Gestation was prolonged from between 1 and 19 weeks in these patients and the gestational age at delivery ranged from 25 to 41 weeks.

Failure of the cerclage was indicated either by the onset of strong contractions or by evidence of infection. We considered the presence of contractions despite tocolysis, a persistent pyrexia, or a C-reactive protein >30 mg/l (normal <10 mg/l) to be indicative of chorioamnionitis. Histological evidence of placental and chorioamniotic infection was found in all the failures, including those in which the first sign of failure was uterine contractions. All of these problems occurred relatively soon after insertion of the suture: <2 weeks in five patients, at 3 weeks in one and at 5 weeks in one. There was also evidence of subclinical maternal or placental infection at delivery between 25 and 32 weeks gestation in five of the successful patients. Infecting organisms included *Escherichia coli*, *G. vaginalis*, *M. hominis*, *Fusobacterium* spp., *Bacteroides* spp., *T. vaginalis* in various combinations.

If infectious complications, prelabour rupture of the membranes or contractions ensued, the suture was removed to allow delivery. In general, the removal of the sutures was uncomplicated but in one patient who had had the suture inserted at full dilatation, strong contractions the next day led to a posterior cervical tear as the suture was removed. The tear was subsequently repaired successfully.

Discussion

These results show that a positive and active approach to cervical dilatation in the midtrimester can lead to delivery of a viable infant. The outcome, had cerclage not been performed, could not have been predicted with certainty in all patients, but in at least one woman with a cervical dilatation of 8 cm at 19 weeks the pregnancy could not have continued without treatment. Prolongation of this pregnancy for 12 weeks following emergency cerclage must have made a significant difference (patient 1). We doubt whether it would be ethical to investigate this technique by a randomized controlled trial.

Using the techniques described, we have been able to avoid failure due to rupture of the mem-

branes at the time of the procedure. This compares very favourably with a 30% rate of rupture of membranes reported by Harger (1980).

The main problem, as described previously by Schulman (1985) and Charles & Edwards (1981), is infection. It is important to exclude infection before insertion of the suture and to take active steps to prevent it thereafter. All the unsuccessful outcomes in this series had evidence of infection. It is disappointing that amniocentesis did not always detect infection where, in retrospect, it was undoubtedly present and that the prophylactic antibiotic regimen which we used does not appear to have helped the outcome. Infection in these women presumably ascended through the partially dilated cervix with colonization of the lower uterine segment followed by penetration of the membranes and amniotic fluid. It is probable that in some pregnancies where we failed to detect infection in the amniotic fluid, it had actually been present in the uterine cavity. Also, it is interesting that in one patient a slowly growing *Fusobacterium* sp. was identified in culture a week after amniocentesis and that this appeared to have been the cause of the clinically detected infection.

We postulate that in some patients who have cervical dilatation in the midtrimester the aetiology is infective even though they may not have pyrexia, uterine tenderness or an obvious purulent vaginal discharge and there may not be demonstrable infection of the amniotic fluid. In these circumstances other methods of detecting infections, such as estimation of C-reactive protein levels, are also likely to be ineffective. It might be expected that antibiotic treatment at the time of the cerclage would eradicate this type of infection in some cases. Our experience has been disappointing in that infection has occurred even when a combination of intravenous antibiotics such as clindamycin and gentamicin has been used in high dosage. It is possible that longer courses of treatment might have been more effective.

It is also important to exclude placental abruption and labour in women with cervical dilatation in the second trimester but we did not find this to be difficult clinically. To this end, a period of observation is helpful before considering emergency cerclage.

We have stopped using Mersilene tape for cerclage because of our anxiety about infective complications and because we suspect that the

interstices of the tape are a breeding ground for bacteria. It seems improbable that monofilament suture material would present the same hazard. We favoured the Wurm technique (Hefner *et al.* 1961) because it is easy and relatively atraumatic. Suturing together the anterior and posterior walls of the cervix is easier than attempting to close the cervix with a purse-string suture, and is more consistent with the normal function of the cervical sphincter (Cousins 1980).

We urge consideration of this technique in women who present with cervical dilatation in the midtrimester of pregnancy who do not have features of placental abruption and who are not in labour. However, we also advise careful bacteriological assessment to exclude subclinical infection before cerclage. By adopting this approach there appears to be little hazard to the woman and an over 50% chance of survival for the infant.

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Platelet reactivity and serum thromboxane B₂ production in whole blood in gestational hypertension and pre-eclampsia

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Abstract

Objective—To determine the nature and extent of changes in platelet reactivity in gestational hypertension and pre-eclampsia (using whole blood techniques which may be more physiological than those previously employed).

Design—Cross-sectional observational study.

Subjects—8 normal primigravidae, 16 women with gestational hypertension and 12 women with pre-eclampsia, studied at around 36 weeks gestation.

Results—Platelet reactivity (aggregation and release reaction) induced by stimulation with adrenaline was decreased in the pre-eclamptic group. Serum thromboxane B₂ production was unchanged in both hypertensive groups compared with the control group.

Conclusions—In the context of evidence of platelet activation in pre-eclampsia, our findings are interpreted as reflecting platelet exhaustion.

It has been suggested that activated platelets are involved in the pathogenesis of gestational hypertension and pre-eclampsia (Wallenburg 1987), and they may contribute to the placental, renal and cerebral damage which occurs in some patients. There have been conflicting reports,

however, concerning platelet reactivity which has been variously shown to be unchanged (Whigham *et al.* 1978) or increased (Morrison *et al.* 1985) in hypertensive pregnancies without significant proteinuria, and unchanged (Inglis *et al.* 1982) or decreased in proteinuric pre-eclampsia (Howie *et al.* 1971; Whigham *et al.* 1978; Splawinska *et al.* 1987).

Pharmacological inhibition of platelet reactivity by low-dose aspirin, which inhibits platelet thromboxane A₂ synthesis, may prevent pre-eclampsia in selected patients (Beaufils *et al.* 1985; Wallenburg *et al.* 1986; Schiff *et al.* 1989). In this study, we have investigated the nature of the changes in platelet reactivity and thromboxane production in patients with gestational hypertension and pre-eclampsia. The whole blood technique which we employed is more physiological than methods using the more conventional platelet-rich plasma which has been employed in the past, as centrifugation, with the removal of both the largest and most active platelets and the inter-active red and white blood cells (Gaarder *et al.* 1961; Blackwell *et al.* 1978)

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is not required. Therefore, we believe that our results more closely reflect the *in vivo* situation, as platelets have been studied in their natural milieu.

Subjects and methods

Eight normal primigravidae had been studied previously, before, during and after pregnancy. They were part of a group of 40 women who were hoping to conceive, recruited from general practice and the hospital sub-fertility clinic. The results of this longitudinal study have been reported (Louden *et al.* 1990) and the data obtained at a mean gestation of 36.5 (range 35.2–37.2) weeks have been used as normal pregnancy controls. In addition, 16 patients with gestational hypertension (GH-group) and 12 with pre-eclampsia (PE-group) were recruited after admission to hospital. It should be noted that *after* venepuncture for this study, 8 of the 16 women with gestational hypertension were treated with 60 mg aspirin daily until delivery, and it is possible that this may have influenced some of the clinical outcome variables in this group. Gestational hypertension was defined as a blood pressure of 140/90 mmHg (Korotkov 4) on at least two occasions 24 h apart, after 20 weeks gestation, in a previously normotensive woman and in whom the blood pressure returned to normal by 3 months after delivery. The blood pressure was measured in the left lateral semi-recumbent position. The definition of pre-eclampsia required, in addition, proteinuria of ≥ 0.5 g/l in a 24 h collection.

The characteristics of the three groups are described in Table 1. All the women in the con-

trol group and in the GH-group were primigravidae; three of the 12 women with pre-eclampsia were multigravid. None of the patients had a history of essential hypertension, renal disease or diabetes, and all pregnancies were singletons. At the time of entry into the study, none of the patients had taken any medication known to influence platelet reactivity, for at least 2 weeks. Apart from eight women in the GH-group, such medication was proscribed for the entire period of study.

Study design

Studies were performed as closely as possible to 36 weeks gestation in the control group, and shortly after admission in the two hypertensive groups. Studies were subsequently repeated at 6 and 12 weeks after delivery.

Experimental technique

The experiments were performed as described previously (Louden *et al.* 1990). The six aggregating agents and their final concentrations in whole blood were: arachidonic acid (AA, 0.2 mM), adrenaline (1 μ M), adenosine diphosphate (ADP, 0.5 μ M), platelet activating factor (PAF, 0.03 μ M), collagen (1 μ g/ml) and U46619 (a synthetic thromboxane mimetic, 0.3 μ M). Saline (150 mM) was used as a control.

Blood collection, platelet aggregation, release reaction and thromboxane B₂ measurements were performed as disclosed previously. In brief, platelet aggregation was measured using a single platelet counting technique after the addition of one of the aggregating agents. The fall in the

Table 1. Age, weight, gestational age and blood pressure in women with gestational hypertension (GH), pre-eclampsia (PE) and normal pregnancy

Variable	GH-group (n = 16)	PE-group (n = 12)	Normal pregnancy (n = 8)
Age (years)	23 (1)	23 (4)	28 (3)
Weight (kg)	74 (4)	68 (7)	73 (5)
Gestational age at entry (weeks)	37.3 (1.5) range 33–40	36.4 (2.4) range 32–41	36.5 (0.7) range 35–37.5
Blood pressure (mmHg)			
At 16 weeks	121 (3) 71 (3)	121 (9) 71 (8)	108 (3) 64 (3)
At time of study	144 (2) 95 (2)	148 (10) 96 (6)	112 (3) 71 (3)
Proteinuria (g/l)	0.04 (0.01)	1.07 (0.2)	—

Results are mean (SD) values

single free platelet count was measured using the Clay Adams Ultra Flo 100 platelet counter, hence the proportion of aggregated platelets was determined. Values were obtained at 10 s intervals for the first minute after addition of the aggregating agent, and also after 2, 4 and 8 min. The release reaction was quantified by measurement of the amount of ^{14}C -labelled serotonin released from prelabelled platelets after platelet aggregation. The serum production of thromboxane B_2 , the major stable metabolite of thromboxane A_2 , was measured using the Amersham International radioimmunoassay kit, following spontaneous clotting at 37°C for 1 h.

Statistical analysis

As the sample size was small, and the data tended not to be normally distributed, medians have been used as the estimate of central tendency for the experimental data, and the 25th and 75th centiles have been used as estimates of the scatter. Mann-Whitney U tests were used where appropriate, thereby avoiding assumptions with regard to the distribution of the data. This test was used because no unpaired non-parametric analysis of variance with repeated measures could be identified. As a consequence, the arbitrary level of statistical significance has been adjusted from $P < 0.05$ to $P < 0.01$, to account for the increased frequency of statistical tests performed.

Results

Clinical outcome

Some features of clinical outcome are described in Table 2. Mean birthweight was significantly reduced ($P < 0.01$) in the PE-group compared with the other two groups. None of the babies in

the control group had a birthweight < 10 th centile for gestational age, but there were two in the GH-group, and seven in the PE-group, two of whom were < 3 rd centile.

Serum urate concentrations were significantly higher in the PE-group than in the other two groups ($P < 0.01$). Four women in the GH-group later developed proteinuria of $> 0.5\text{ g}/24\text{ h}$, whilst the mean amount of proteinuria in the PE-group rose to 1.35 (SE 0.6) g/l before delivery. There were no neonatal deaths, and no patient developed thrombocytopenia ($< 100 \times 10^9/\text{l}$), or any clinical evidence of a bleeding tendency. The mean platelet count was significantly reduced in the PE-group (205, SD 55) compared with both the controls (279, SD 94) and the GH-group (268, SD 55) ($P < 0.01$), but increases in the platelet distribution width (controls: 17.4, SD 0.3; GH-group: 17.3, SD 0.7; PE-group: 17.8, SD 0.9) and mean platelet volume (controls: 10.0, SD 2.1; GH-group: 9.5, SD 0.7; PE-group: 10.6, SD 1.4) were not significant.

Platelet aggregation

With the exception of results obtained when adrenaline was used as the aggregating agent, no significant differences in platelet aggregation were found between either of the hypertensive groups and the control group, at any of the time points studied. Using adrenaline as the aggregating agent, median platelet aggregation was greatest in the control group, less in the PE-group, and least in the GH-group (Fig. 1a). However, the scatter of the data was greatest in the GH-group, and least in the control group, and as a consequence, a statistically significant reduction in adrenaline-induced platelet aggregation, compared with normal pregnancy, was seen only in the PE-group, 4 min after the addition of the aggregating agent ($P < 0.01$).

The four patients in the GH-group who later

Table 2. Pregnancy outcome in women with gestational hypertension (GH), pre-eclampsia (PE) and normal pregnancy

	GH-group ($n = 16$)	PE-group ($n = 12$)	Normal pregnancy ($n = 8$)
Birthweight (kg)	3.13 (0.21)	2.18 (0.73)	3.13 (0.25)
Gestational age at delivery (weeks)	38.4 (2.5) range 34–40	37.0 (2.5) range 34–41	39.0 (0.6) range 36–42
Serum urate ($\mu\text{mol}/\text{l}$)	302 (65)	386 (64)	212 (73)
Platelet count ($10^9/\text{l}$)	268 (64)	205 (62)	279 (94)

Results are mean (SD) values.

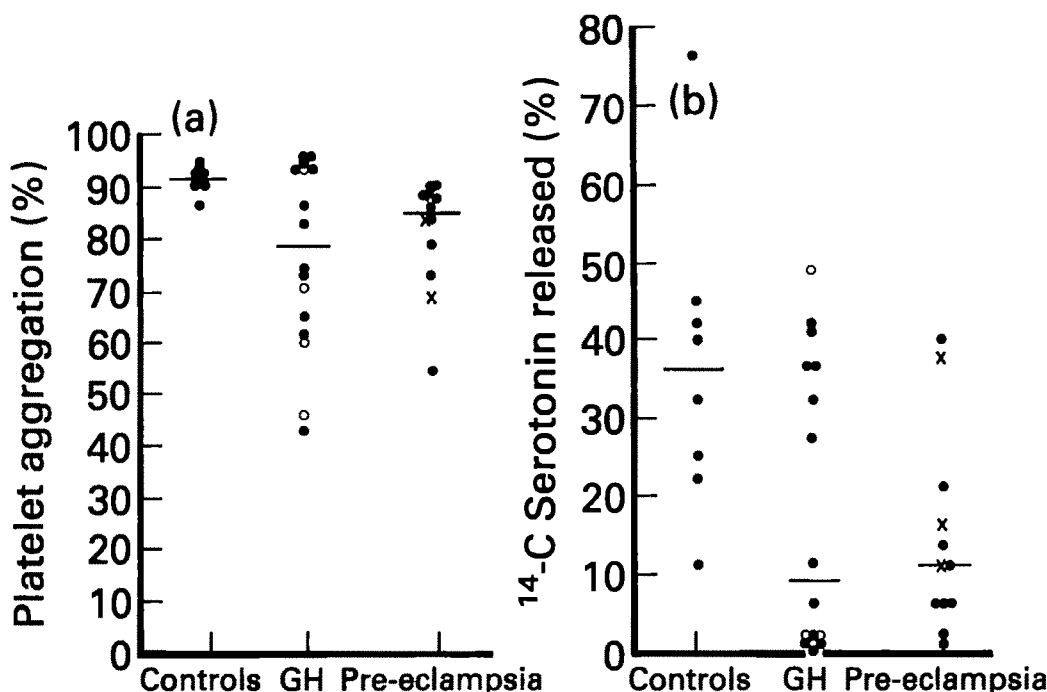


Fig. 1. Plate reactivity (after 4 min) in response to 1 μ M adrenaline in normal pregnancy (controls), gestational hypertension (GH) and pre-eclampsia (PE). Median values are shown.

(1a). Platelet aggregation. The decreased aggregation was statistically significant ($P < 0.01$) in the PE-group.

(1b). Platelet release reaction. The decreased release was statistically significant ($P < 0.01$) in the PE-group.

Open circles have been used to denote those patients in the GH-group who later developed proteinuria of >0.5 g/24 h. Crosses have been used to denote the multiparous patients in the PE-group.

developed significant proteinuria (shown as open circles in Fig. 1) could be considered as 'early pre-eclampsia' rather than simple gestational hypertension, and transferred to the PE-group for analysis. When this is done, median platelet aggregation is less in the extended PE-group than in the abbreviated GH-group.

As some authors distinguish between the 'true' pre-eclampsia of the primigravida, and that seen in multigravidae, where other causes have been implicated, consideration has been given to the results in the PE-group when multigravidae (shown as crosses in Fig. 1) are excluded. Such an exclusion did not affect the interpretation of the results of the PE-group.

Release reaction

No statistically significant differences were seen with any of the aggregating agents other than adrenaline. The release reaction was greatest in the control group (36%), less in the PE-group (11%), and least in the GH-group (9%). The reduction in the adrenaline-induced release

reaction was only statistically significant in the PE-group ($P < 0.01$) but not in the GH-group ($0.01 < P < 0.05$) compared with the control group (Fig. 1b). When the patients in the GH-group who subsequently developed proteinuria (shown as open circles in Fig. 1b) were transferred to the PE-group, the median values changed to 19% in the GH-group and 9% in the PE-group. Exclusion of the three multigravidae (shown as crosses in Fig. 1b) from the PE-group did not alter the interpretation of the results. There were no differences in platelet aggregation or the release reaction between the three groups at either 6 or 12 weeks after delivery.

Serum thromboxane B_2 production

This was unchanged in either of the hypertensive groups, at 36 weeks gestation, and at both 6 and 12 weeks after delivery. At 36 weeks, median (25th centile, 75th centile) values were as follows: control-group: 0.63 (0.45, 1.05); GH-

group: 0.72 (0.42, 0.95); PE-group: 0.70 (0.40, 0.95) nmol thromboxane B₂ per platelets $\times 10^9$.

Discussion

The hypertensive disorders of pregnancy have been associated with increased platelet reactivity, and this topic has been reviewed (Wallenburg 1986). Platelet lifespan decreases as the mean platelet volume increases, and a reduction in the platelet count results. Increased platelet secretion of beta-thromboglobulin and adenine nucleotides, and enhanced reactivity of the platelet cyclo-oxygenase pathway have been interpreted as corroborative evidence of platelet activation in pre-eclampsia. Moreover, recent studies have shown that the use of anti-platelet agents may prevent pre-eclampsia in selected patients (Beaufils *et al.* 1985; Wallenburg *et al.* 1986; Schiff *et al.* 1989).

In contrast to evidence of platelet activation in pre-eclampsia, we have demonstrated reduced platelet aggregation and release reaction in these patients, despite a fall in the platelet count. We believe that the likeliest explanation for this apparently conflicting evidence of decreased platelet reactivity and presumed platelet consumption has occurred because the platelets from the pre-eclamptic women were already 'exhausted' at the time of sampling. The platelets may become activated in the uteroplacental circulation, aggregate, discharge their intracellular granules, and subsequently return to the systemic circulation, relatively inert because of empty stores of pro-aggregatory substances with which to mount an aggregatory response (O'Brien 1978). Patients with gestational hypertension who went on to develop pre-eclampsia tended to have less active platelets than those who did not. We would interpret this as platelet exhaustion preceding the onset of proteinuria.

An alternative hypothesis is that the changes we have observed may represent the loss of the most active platelets from the circulation because of prior aggregation *in vivo*, leaving a relatively inactive subpopulation available for study. The decreased reactivity seen in women with pre-eclampsia is unlikely to be due to decreased sensitivity of the platelets to either the non-specific stimulation of the experimental protocol, mediated by the release of ADP from erythrocytes (Fox *et al.* 1982), or to a decreased

sensitivity to thromboxane A₂, as no significant changes in either platelet aggregation or release reaction were observed when either saline or U46619 were employed as the aggregating agent. However, such effects cannot be ruled out when only small samples are used.

The only previous report of platelet reactivity in whole blood in pre-eclampsia suggested that ADP-induced platelet aggregation was greater than in normal pregnancy at about 32 weeks gestation (Greer *et al.* 1988). That we found no such difference in the present study may be explained on two counts; our patients had less severe disease, and we used a concentration of 0.5 μ M, whereas concentrations of 2 μ M and 5 μ M were used in the previous study. It is interesting to note that ADP-induced platelet aggregation does not depend on the synthesis of thromboxane A₂ at the dose we employed.

In the present study we found no difference in serum thromboxane B₂ production between the hypertensive and normotensive women and this is in agreement with others (Pekonen *et al.* 1986). This does not, however, preclude an increased thromboxane A₂ synthesis *in vivo*, as our technique measures the maximal production of the major stable metabolite of the active eicosanoid, and can in no way be interpreted as a 'circulating level'. Increased plasma concentrations of thromboxane B₂ have been described in women who develop pre-eclampsia (Greer *et al.* 1985), possibly reflecting *in vivo* platelet thromboxane A₂ production. The recent demonstration of increased thromboxane A₂ synthesis in pre-eclampsia (Fitzgerald *et al.* 1990), using the 'gold standard' technique of negative ion mode gas chromatography mass spectrometry of urinary metabolites, tends to support this suggestion.

In conclusion, we have demonstrated decreased platelet reactivity in women with pre-eclampsia which has been confined to those pathways dependent, at least in part, on the cyclo-oxygenase pathway leading to thromboxane A₂ release. In the context of considerable evidence of platelet activation in hypertensive pregnancies, this has been interpreted as evidence of platelet exhaustion. It remains to be seen whether pharmacological inhibition of platelet thromboxane A₂ synthesis with aspirin is able to prevent this postulated activation and exhaustion cycle, an action which could explain the observed effectiveness of this therapeutic regimen for the prevention of pre-eclampsia.

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Is oral contraceptive use still associated with an increased risk of fatal myocardial infarction? Report of a case-control study

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Abstract

Objective—To investigate the association between fatal myocardial infarction and use of modern low-dose oral contraceptives.

Design—A case-control study.

Setting—General practices throughout England and Wales.

Subjects—161 women aged under 40 dying from myocardial infarction during 1986–1988. Living controls (2 per case), matched for age and marital status, were chosen from general practice lists. Information was collected during structured interviews with general practitioners, and from postal questionnaires sent to surviving partners of the cases and to control women.

Main outcome measures—Mortality from myocardial infarction in relation to many risk factors, notably oral contraception, as measured by relative risk.

Results—After allowing for the confounding effects of medical risk factors and for surgical sterilization, the overall relative risk associated with both current and past use of oral contraceptives was estimated to be 1.9 (95% CI 0.7 to 4.9, and 1.0 to 3.5 respectively). The relative risk associated with current use of preparations containing 50 µg of oestrogen, however, was estimated to be 4.2 (0.5 to 39.2). At least some of the relative risk associated with oral contraceptive use is likely to be attributable to the confounding effect of cigarette smoking, but it is impossible to estimate how much from the available data.

Conclusions—If there was an increased risk of fatal myocardial infarction associated with oral contraceptive use in 1986–1988 it is likely to have been less than two-fold; in this study risks were slightly, but not significantly, elevated with both current and previous use. It may be that any increase in risk is associated solely with the older combined preparations containing 50 µg of oestrogen.

Epidemiological studies have shown oral contraceptive use to be associated with an increase in

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the risk of both fatal and non-fatal myocardial infarction. The studies of the 1960s and 1970s have been reviewed extensively (Vessey 1980; Dalen & Hickler 1981; Stadel 1981). During the 1980s a series of case-control studies conducted in Britain (Adam *et al.* 1981), elsewhere in Europe (La Vecchia *et al.* 1987; Ananjevic-Pandey & Vlainiac 1989), and in the United States (Talbot *et al.* 1989; Krueger *et al.* 1980; Rosenberg *et al.* 1980) found relative risks of myocardial infarction associated with recent use of oral contraceptives ranging between 1.2 and 3.5. Analyses of laboratory based studies have indi-

cated that the adverse effects of different oral contraceptives on cardiovascular risk factors are related to the types and doses of both oestrogen and progestogen contained in the preparations (Fotherby 1990; Gaspard 1987; Bonnar 1987). Over the last 10 years the formulation of oral contraceptive preparations has changed with the introduction of new progestogens and a trend towards lower doses of both oestrogen and progestogen. Moreover, the pattern of use of oral contraceptives has also changed, with a decline in use among women over 30 (who are at greater risk of myocardial infarction) and an increasing tendency for older women to select progestogen only preparations (Thorogood & Vessey 1990). In addition, increasing knowledge among health professionals of the effects of oral contraceptives has probably led to better selection of potential oral contraceptive users on the basis of medical history, and to better supervision of users during follow-up. For all these reasons both the absolute and relative risk of myocardial infarction associated with use of oral contraceptives may have declined. We describe a case-control study of fatal myocardial infarction undertaken to examine this hypothesis.

Subjects and methods

Identification of cases

The study described here formed part of a larger study of mortality from cardiovascular disease, including myocardial infarction, cerebrovascular accident and venous thromboembolism. All deaths occurring in England and Wales among women aged 16–39 between January 1986 and December 1988 where the underlying cause of death was coded as myocardial infarction (ICD code 410, 9th revision) were considered for inclusion in the study. Death certificates were supplied by the Office of Population Censuses and Surveys. The cause of death was verified (or otherwise) by requesting copies of post-mortem reports and relevant hospital records, which were then examined (either by J.M. or M.M.) to determine the cause of death. A death was defined as being due to myocardial infarction on the basis of a post-mortem report, a positive ECG report or evidence of enzyme changes. Such deaths form the basis of this report.

Cases were excluded from the study if there was insufficient evidence to confirm the cause of

death. Cases were also excluded if the woman had been resident for at least 1 month in an institution, or if she had been pregnant within the last 2 months before death. Deaths that were preceded by another life threatening illness such as advanced cancer were also excluded.

Selection of controls and ascertainment of clinical data

With the assistance of local Family Practitioner Committees and the National Health Service Central Register, an attempt was made to trace the general practitioner of each case that was included, and he or she was interviewed using a structured questionnaire by a part-time medical officer employed by the Committee on Safety of Medicines. Two control women, matched for age (within 5-year groups) and marital status (two categories: currently married or living as married, or not) were selected randomly from the practice records of the same general practitioner. The procedure was similar to that described for control selection in our earlier studies (Mann & Inman 1975). The same criteria for exclusion were applied as for the cases, and a similar questionnaire was completed for the control women. In a few cases, controls were excluded at the analysis stage because they fell within the exclusion criteria (for example, controls who appeared by backward calculation to have been pregnant at the time of death of the relevant matched case). Three cases had no matched controls. The identity of the control women was not recorded on the completed questionnaires in the interests of confidentiality.

The general practitioners were asked for details of past medical history (including any diagnosis of cardiovascular disease, hypertension, or diabetes), drug history (particularly use of oral contraceptives), menstrual status, obstetric history, contraceptive methods, parity, height, weight, blood pressure and smoking habits.

Postal questionnaire data

Additional information concerning smoking habits was obtained from postal questionnaires. If the case was married or living as married and the general practitioner knew the whereabouts of the surviving partner, a brief questionnaire relating mainly to smoking but also to oral contraceptive use and certain other matters was sent

both to the surviving partner and to the corresponding pair of control women. The control women were assured in the accompanying letter that the questionnaire was anonymous and that their identity was known only to their general practitioner, who posted the letter at our request. If no reply was received one reminder was sent by the same method. A previous study had been conducted to test the reliability of data about a woman's smoking habit and oral contraceptive use provided by her husband (Thorogood & Vessey 1989). This study demonstrated good agreement between husband and wife regarding smoking habit. Husbands usually reported accurately on whether or not their wives were current or past users of oral contraceptives but were generally unable to give more accurate details of use.

Analysis

A single smoking variable was constructed using the data available both from the postal questionnaire and from the general practitioner's notes. There was adequate agreement between postal questionnaire reports and general practitioner information on smoking habits, except that the general practitioners reported fewer women to be ex-smokers. If information on smoking was available from a postal questionnaire, the constructed variable took that value. If, however, a postal questionnaire had not been received for a particular woman and the general practitioner had provided information about smoking, the constructed smoking variable took that value.

A woman was defined as having diabetes if the general practitioner reported such a diagnosis. A diagnosis of hypertension was defined as a report of such a diagnosis or a record in the general practice notes of a prescription for hypotensive medication.

Oral contraceptive use was assigned to one of three categories: use in the month before death (or the corresponding time for the controls), described in this paper as current use; use in the preceding 10 years but not the last month, described in this paper as previous use; and no use within 10 years; including women who had never used oral contraceptives), described in this paper as non-use.

Data were entered on a personal computer using dBASE, and then transferred to the University of Oxford VAX cluster. Simple two and three way tables were constructed and χ^2 values calculated using SPSSX. Relative risks were esti-

mated by conditional logistic regression analysis adjusting for the effects of matching (Breslow & Day 1980) using the computer software EGRET (Anonymous 1989) to estimate odds ratios, which approximate closely to relative risks. The power of the study was estimated using the computer software EPILOG POWER (Anonymous 1987).

Ethical approval

The study was approved by the Central Oxford research ethics committee.

Results

Table 1 shows the number of cases of myocardial infarction considered for entry into the study together with the reasons why some cases were excluded. There were 184 cases eligible for inclusion and 23 (13%) were excluded for administrative reasons. In total 161 cases of myocardial infarction were included in the study. There were 99 cases where the general practitioner knew of a surviving partner and agreed to send postal questionnaires to him and to the two matched control women. Forty-seven (47%) partners and 133 (67%) of the control women returned completed questionnaires.

Table 2 shows the numbers of cases and controls with a relevant past medical history. Substantially more previous morbidity was reported amongst the cases than the controls. A single dichotomous variable was constructed to represent the presence or absence of at least one of the known clinical risk factors for myocardial infarction. These risk factors were defined as a diagnosis of diabetes, hyperlipidaemia, hyper-

Table 1. Death certificates received, numbers considered for entry into the study and reasons for exclusion

Certificates received	215
Reasons for exclusions:	
Pregnant or within 2 months post-partum	6
Resident in an institution	6
Already gravely ill with cancer, renal failure or neurological disease	4
Diagnosis not confirmed	15
Considered for entry into the study	184
Medical notes lost	7
General practitioner not traced	6
PTMO unable to obtain interview with GP	10
Total included	161

Table 2. Number and percentage of cases of myocardial infarction and controls reported to have a history of certain diagnoses

Diagnosis	Numbers and percentages with diagnosis		
	Cases (<i>n</i> = 161)	Controls (<i>n</i> = 309)	<i>P</i>
Previous myocardial infarction	11 (7)	—	<0.001
Angina pectoris	12 (8)	—	<0.001
Cerebrovascular accident	5 (3)	—	<0.01
Pulmonary embolism	4 (3)	—	<0.05
Superficial venous thrombosis	6 (4)	4 (1)	—
Deep venous thrombosis	5 (3)	—	<0.01
Hypertension when not pregnant	29 (18)	7 (2)	<0.001
Hypertension during pregnancy	26 (16)	20 (7)	<0.01
Other heart or blood vessel disease	14 (9)	4 (1)	<0.001
Diabetes mellitus	22 (14)	2 (1)	<0.001
Hyperlipidaemia	6 (4)	—	<0.001
Surgical operation or accident within 3 months of death	9 (6)	3 (1)	<0.01
Any other major illness	63 (39)	65 (21)	<0.001

Significance of difference between cases and controls estimated by χ^2 test ignoring matching.

tension, angina or a previous recorded myocardial infarction. Fifty-four cases (34%) and 9 controls (3%) had at least one risk factor; on this basis the estimated relative risk of a myocardial infarction associated with the presence of at least one risk factor was 7.6 (95% CI 4.4 to 13.2, analysis based on 158 case-control sets).

The smoking habits of the cases and controls as described by the general practitioners, by the postal questionnaires, and by the constructed smoking variable are shown in Table 3. The relative risk of a myocardial infarction associated with current cigarette smoking as defined by the constructed smoking variable compared with never smoking was estimated to be 19.3 (95% CI 6.0 to 62.5, analysis based on 70 case-control sets).

The use of oral contraceptives amongst the cases and controls as reported by general practitioners is shown in Table 4. There was a slight excess of users amongst the cases, but the difference was not significant. The relative risk of myocardial infarction associated with current use of oral contraceptives compared with non-use was estimated to be 1.1 (95% CI 0.6 to 2.4, analysis based on 89 case-control sets). The relative risk associated with previous use compared with non-use was estimated to be 1.4 (0.9 to 2.4, analysis based on 117 case-control sets).

Women who are no longer at risk of pregnancy, either because they have had a tubal liga-

tion or hysterectomy or because their partner has had a vasectomy are unlikely to be using oral contraceptives. Moreover, women already at risk of myocardial infarction because of serious medical conditions might have been advised not to use oral contraceptives. Table 5 shows the use of oral contraceptives amongst women at risk of pregnancy, amongst women without medical risk factors for myocardial infarction, and amongst women both without risk factors and at risk of pregnancy. There is a small excess of use, both current and previous, amongst the cases in all three categories. When women with medical risk factors were excluded from the analysis there was a significant difference in oral contraceptive use between the cases and controls, using a simple χ^2 -test not allowing for the effect of matching. When the analysis was carried out by conditional logistic regression, the relative risk of myocardial infarction associated with current use of oral contraceptives compared with non-use allowing for the effects of surgical sterilization and medical risk factors was 1.9 (95% CI 0.7 to 4.9, analysis based on 89 case-control sets). The corresponding relative risk associated with previous use was also 1.9 (1.0 to 3.5, *P* = 0.054, analysis based on 117 case-control sets).

Table 6 shows the use of oral contraceptives in three smoking history categories amongst women who had not been surgically sterilized

Table 3. Smoking habits of cases and controls as reported by general practitioners and in postal questionnaires (percentages in parentheses)

	Cases	Controls
General practitioner reported:		
Non-smoker	18 (15)	96 (68)
Past smoker	10 (8)	6 (4)
Current smoker	93 (77)	40 (28)
Total	121 (100)	142 (100)
Smoking habits not known	40 (25% of cases)	167 (54% of controls)
Surviving partner/control woman reported:		
Non-smoker	4 (9)	70 (54)
Past smoker	7 (16)	25 (19)
Current smoker	33 (75)	35 (27)
Total	44 (100)	130 (100)
No report	117 (73% of cases)	179 (58% of controls)
Constructed smoking variable:		
Non-smoker	20 (15)	120 (57)
Past smoker	15 (11)	30 (14)
Current smoker	99 (74)	61 (29)
Total	134 (100)	211 (100)
Smoking habits not known	27 (17% of cases)	98 (32% of controls)

χ^2 -test ignoring matching on difference between cases and controls $P < 0.001$ for all three variables.

and who did not have medical risk factors for myocardial infarction and for whom a smoking history was available. There was a slight excess of current oral contraceptive use amongst cases in each smoking category. Estimation of relative risk by conditional logistic regression proved to be impossible for current oral contraceptive use, because there were too few case-control sets available for analysis. However, the relative risk associated with current and previous use considered together compared with non-use adjusting for surgical sterilization, medical risk factors, and current cigarette smoking was 1.1 (0.3 to 3.8, analysis based on 70 case-control sets).

Table 7 shows the types of oral contraceptive being used by cases and controls who were currently using an oral contraceptive. There were more than three times as many cases using preparations containing 50 µg of oestrogen com-

Table 4. Oral contraceptive use in cases and controls as reported by general practitioners (percentages in parentheses)

Oral contraceptive use	Cases	Controls
Non-use	66 (41)	143 (46)
Previous use	58 (36)	109 (35)
Current use	37 (23)	57 (19)
Total	161 (100)	309 (100)

Table 5. Use of oral contraceptives as reported by the general practitioners in women at risk of pregnancy and women without medical risk factors for myocardial infarction (percentages in parentheses)

Oral contraceptive use	Cases	Controls
Women assumed at risk of pregnancy		
Non-use	43 (37)	110 (46)
Previous use	37 (32)	72 (30)
Current use	36 (31)	56 (24)
Total	116 (100)	238 (100)
Women without risk factors for myocardial infarction*		
Non-use	31 (33)	133 (47)
Previous use	36 (39)	98 (35)
Current use	26 (28)	53 (19)
Total	93 (100)	284 (100)
Women assumed at risk of pregnancy and without risk factors for myocardial infarction*		
Non-use	20 (29)	104 (47)
Previous use	24 (35)	65 (29)
Current use	25 (36)	52 (24)
Total	69 (100)	221 (100)

Note: risk factors defined as: hypertension (including during pregnancy), hyperlipidaemia, diabetes, angina, or a previous myocardial infarction

* χ^2 -test ignoring matching for difference between cases and controls $P < 0.05$ (2 df).

Table 6. Use of oral contraceptives as reported by general practitioners among women assumed at risk of pregnancy and without risk factors for myocardial infarction in different smoking groups (as defined by constructed variable)

Oral contraceptive use	Cases	Controls
Never smoked		
Non-use	3 (43)	48 (59)
Previous use	2 (29)	20 (24)
Current use	2 (29)	14 (17)
Total	7 (100)	82 (100)
Smoked in past		
Non-use	1 (25)	7 (30)
Previous use	1 (25)	8 (35)
Current use	2 (50)	8 (35)
Total	4 (100)	23 (100)
Current smokers		
Non-use	12 (27)	14 (36)
Previous use	14 (32)	12 (31)
Current use	18 (41)	13 (33)
Total	44 (100)	39 (100)

pared with the controls, but only about half as many cases using progestogen only preparations. These differences were not statistically significant. The relative risk associated with current use of a 50 µg preparation (compared with current use of any other preparation or non-use of any preparation) was estimated to be 4.2 (0.5 to 39.2, analysis based on 89 case-control sets). It is possible that the higher dose 50 µg preparations were used more by older women who were reluctant to change to a more modern pill, and the incidence of myocardial infarction is strongly age related. Thus, although the controls were matched with the cases within 5-year age groups, it is possible that the increased use of 50 µg preparations by the cases is attributable to the cases being a year or two older on average than the controls. The data do not, however, support this idea: the ages of the five cases using 50 µg combined preparations were 27, 30, 31, 33 and 35, while the two controls using such preparations were aged 34 and 35.

There was no evidence in the data of any trend in risk associated with duration of use of oral contraceptives or with time since last used.

Information on oral contraceptive use was also collected on the postal questionnaire, although the amount of information available was very limited because the relatively small proportion of subjects completing the postal questionnaire. However, information was avail-

able for 43 (27%) cases and 129 (42%) controls. Five (12%) of the cases and 8 (6%) of the controls were reported to be current oral contraceptive users, while 15 (35%) of cases and 51 (40%) of controls were reported to be previous users. The estimated relative risk of current oral contraceptive use compared with non-use from these data was 1.2 (0.2 to 8.6, analysis based on 10 case-control sets) and the corresponding relative risk for previous use was 0.5 (0.2 to 1.3, analysis based on 33 case-control sets).

There were no significant differences in the number of pregnancies experienced by cases and controls, nor in the proportion where either the woman or her partner had been surgically sterilized, nor in the proportion of women who had a history of using female sex hormones other than oral contraceptives.

Discussion

The results of this study indicate a greatly elevated risk of fatal myocardial infarction associated with medical risk factors including a history of hypertension in pregnancy, other hypertension, hyperlipidaemia, and diabetes. Cigarette smoking also appears to be associated with a very large relative risk of myocardial infarction of around 19-fold. By contrast, the relative risk of myocardial infarction associated with both current and past use of oral contraceptives as recorded by the general practitioner was only slightly increased, and was not statistically significant. After allowing for the confounding effects of medical risk factors and for surgical sterilization, the relative risk of both current and previous use was estimated to be 1.9 (95% CI 0.7 to 4.9, and 1.0 to 3.5 respectively).

Because of the limited amount of data on smoking, it is not possible to make any definite

Table 7. Types of preparation in use by those women currently using oral contraceptives (percentages of all cases/controls in parentheses)

Type of preparation	Cases	Controls
Combined preparation		
With 50 µg oestrogen	5 (3.1)	2 (0.6)
With 20–35 µg oestrogen	19 (11.8)	27 (8.7)
Bi- or tri-phasic preparations	9 (5.6)	13 (4.2)
Progestogen only preparations	3 (1.9)	12 (3.9)
Preparation not known	1 (0.6)	3 (1.0)
Total users within 1 month of death	37 (23.0)	57 (18.4)

statement about the relation between smoking and oral contraceptive use as risk factors. There is no evidence from Table 6 that the excess of oral contraceptive users amongst the cases was confined to cigarette smokers, but the conditional logistic regression analysis of oral contraceptive use suggested that most of the effect was attributable to smoking.

There is a possibility that any increase in risk associated with current oral contraceptive use may be concentrated in users of the older high-dose combined preparations containing 50 µg of oestrogen, but the study is too small for this to be confirmed.

Sending postal questionnaires to widowers and to control women was a new idea, tried for the first time in this study. While the replies did provide some additional information on the smoking habits of the women, there were problems with the postal questionnaire. The response rate, even after one reminder, was poor for the widowers (47%) although rather better for the control women (67%). A particular problem was encountered with the postal replies to the question about oral contraceptive use, which showed limited agreement with the corresponding information reported by general practitioners. General practitioner records have been shown not to provide a complete record of oral contraceptive use (UK National Case-control Study Group 1989), but even during careful personal interview, women may give incorrect contraceptive information (Coulter *et al.* 1986) and in this study there was only one very brief question about pill use (which was not optimally worded) on a postal questionnaire. Furthermore, the postal questionnaires were often sent out many months after the case died, and this produced confusion over time relationships between events of interest and contraceptive use. For these reasons, we have little confidence in the questionnaire information on oral contraceptive use and have focused mainly on the general practitioner information in this report, despite its known shortcomings. However, analysis of the small amount of data available from the postal questionnaires did not indicate an increase in risk associated with either current or past use of oral contraceptives.

Because of the commonly known hypothesis of the study, and the way that the controls were selected, it was not possible to blind interviewers or general practitioners either to the hypothesis or to whether a woman was a case or control.

However, the data collected at the interview were taken direct from contemporary medical records, so that bias in recall should have been avoided. Moreover, an almost identical questionnaire was used to obtain information from general practitioner records for cases and controls, so any bias in providing information about dead and living women should have been minimized.

A nested case-control analysis of non-fatal myocardial infarction in the Oxford/FPA cohort study found a six-fold increase in risk associated with cigarette smoking as recorded at recruitment (Mant *et al.* 1987), while two case-control studies of non-fatal myocardial infarction, one in Italy (La Vecchia *et al.* 1987) and one in Yugoslavia (Ananjevic-Pandey & Vlainjac 1989) found relative risks of 8 and 3 respectively associated with smoking more than 15 cigarettes a day. The finding of a 19-fold increase in risk of fatal myocardial infarction associated with cigarette smoking in this study should be interpreted with some caution since smoking information was not available for 17% of the cases and 32% of the controls, and it may well be that there is a systematic bias in favour of recording positive smoking histories by general practitioners. Nevertheless, the excess in risk is evident with all three smoking variables, and is large. Even in the extreme case, assuming that all the remaining women for whom smoking history as defined by the constructed variable was not known were non-smokers, the relative risk associated with current cigarette smoking would be greater than 7.

The principal purpose of this study was to re-examine the relation between fatal cardiovascular disease and use of oral contraceptives, the hypothesis being that the risk of such disease would have reduced from that observed in earlier studies as a result of changes in types of preparations and patterns of use. Recent case-control studies of myocardial infarction have found relative risks associated with current oral contraceptive use ranging between 1.1 and 3.5 in all women and between 1.4 and 3.9 in women with no other risk factors (Adam *et al.* 1981; Ananjevic-Pandey & Vlainjac 1989; Krueger *et al.* 1980; La Vecchia *et al.* 1987; Rosenberg *et al.* 1980; Talbott *et al.* 1989). While most epidemiological studies have failed to find any increase in risk associated with past use of oral contraceptives, in two recent European studies (La Vecchia *et al.* 1987; Ananjevic-Pandey & Vlainjac

1989) increased risks of 1.8 and 2.4 respectively were found to be associated with such use. An earlier case-control study from the United States (Slone *et al.* 1981) also found an elevated risk amongst women aged over 40 who had used oral contraceptives for >5 years in the past (relative risk 1.6, 95% CI 1.1 to 2.5), but a more recent case-control study from the same group (Rosenberg *et al.* 1990) failed to find any significant increase in risk associated with such use (relative risk 1.1, 95% CI 0.8 to 1.5). An analysis of mortality from the Oxford/FPA cohort study, albeit based on small numbers, found an excess mortality from ischaemic heart disease in the women most recently using oral contraceptives which was also apparent in those stopping the pill ≥ 6 years before the fatal event (Vessey *et al.* 1989).

The power of the present study was such that the minimum significant increased relative risk associated with oral contraceptive use that could have been detected with 90% certainty was 1.8 for any use in the last 10 years and 2.1 for current use. The simple relative risks associated with current use or other use within 10 years were all well below this, although above 1, and even after adjusting for the presence of risk factors and contraindications to oral contraceptive use they were still below 2, and were not statistically significant. If there is an increased risk of fatal myocardial infarction associated with modern oral contraceptive use, it is likely to be less than two-fold, and seems to be associated with both current and previous use in this study. This study was limited to fatal myocardial infarction, and the results cannot necessarily be extended to the risks of non-fatal disease.

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Conservative laparoscopic treatment of ectopic pregnancies using the CO₂-laser

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Abstract

Objective—To assess the feasibility of CO₂-laser-endoscopic surgical treatment for large and/or ruptured ectopic pregnancies, and to compare the results with those of microsurgical salpingotomy.

Design—A retrospective review of all women treated for an ectopic pregnancy during a 6-year period, 1984-1989. During 1988 and 1989 treatment was randomized by the day of admission, depending only upon the surgeon in charge, some performing a linear salpingotomy ($n=42$) and some a CO₂-laser laparoscopy ($n=34$) in all women haemodynamically stable.

Setting—Department of Obstetrics and Gynaecology, University Hospital Gasthuisberg, Leuven.

Subjects—135 women with ectopic pregnancies of whom 76 were included in the randomized series between 1988 and 1989. Overall 11 were treated by pelvic lavage, 78 by laparotomy and 46 by laparoscopic procedures.

Main outcome measures—Postoperative complications, duration of hospital stay. Cumulative pregnancy rates after the procedures.

Results—The two groups of women analysed in the randomized series were comparable for duration of amenorrhoea, diameter of the ectopic pregnancy and prevalence of 'ruptured' ectopics, but the duration of stay in hospital was much shorter (mean 2.9, SD 1.8 days) for the 34 women treated by laparoscopy than for the 42 women treated by laparotomy (mean 6.8, SD 1.6 days). The post-operative cumulative pregnancy rate was higher in nulliparous women with a history of infertility or pelvic inflammatory disease (PID), when treated with CO₂-laser-laparoscopy ($P=0.009$). The recurrency rate was low (<5% in both groups). Overall in the women treated by laparotomy, postoperative cumulative pregnancy rates were lower following excision or adnexectomy than after a microsurgical linear salpingotomy ($P=0.01$). Four women treated by laparoscopy required a second procedure.

Conclusion—Endoscopic treatment of large and/or ruptured ectopic pregnancies is feasible and resulted in a shorter hospital stay and, in nulliparous women with a history of PID or infertility, in higher cumulative pregnancy rates, than after microsurgical salpingotomies.

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The early diagnosis of ectopic pregnancies has stimulated conservative microsurgical treatment (DeCherney & Diamond 1987; Langer *et al.* 1982; Oelsner *et al.* 1987). This trend is extending to endoscopic surgery.

The feasibility of the endoscopic treatment of ectopic pregnancies by (partial) salpingectomy (Dubuisson *et al.* 1987; Tarasconi 1981) or by linear salpingotomy (Brumsted *et al.* 1988; DeCherney & Diamond 1987; Henderson 1989; Johns & Hardie 1986; Mäkinen *et al.* 1989;

Mecke *et al.* 1989; Pouly *et al.* 1986; Vermesh *et al.* 1989) has been widely established. It is not yet clear, however, whether endoscopic treatment should be limited to the small and/or unruptured ectopic pregnancies, whether minimal surgery, that is linear salpingotomy and extraction, should be preferred over a partial resection in all cases, and how the long term results of endoscopic surgery compare with the microsurgical treatment and with nonsurgical therapies (Shapiro 1987; Stovall *et al.* 1989).

Since 1990 laparoscopic treatment of ectopic pregnancies has become usual in our department, almost entirely replacing microsurgery. During 1988–1989 some physicians used a laparoscopic method for all their patients whereas others used a laparotomy and microsurgery. These data are reviewed to compare and to analyse critically the results of microsurgical and laparoscopic treatment.

Patients and methods

All 135 women treated for an ectopic pregnancy in the department of obstetrics and gynaecology, University Hospital Gasthuisberg, between 1 January 1984 and 1 December 1989 were included in this study. Early diagnosis was made by a combination of clinical examination, hCG assays and echography. Between 1984 and 1987 echography was performed abdominally, and since 1988 mostly with a vaginal probe.

Before 1988 laparoscopic treatment was performed by some surgeons in selected patients. To examine the feasibility of endoscopic surgery for all patients, a prospective trial was set up by some surgeons (P.K., C.M.). In 1988 and 1989 they treated all women with ectopic pregnancies, who were haemodynamically stable, by laser-endoscopy, whereas the other consultants of the department continued to use microsurgery. During 1988 and 1989 the selection of the treatment thus depended only upon the day of admission and the gynaecologist in charge. This series therefore can be considered as randomized by the day of admission, for comparison of endoscopic and microsurgical treatment.

All women with a haemoperitoneum of >0.5 litres were considered as 'ruptured'. In order to interpret the postoperative pregnancy rates the following risk factors were taken into account: age, parity (nulligravidae $n=47$) and a history of infertility for more than 1 year ($n=37$), tubal or other abdominal surgery ($n=29$), pelvic inflam-

matory disease (PID) ($n=29$), and the use of an intrauterine contraceptive device (IUCD, $n=18$) (Torburn *et al.* 1988).

Assays

Human chorionic gonadotrophin (hCG) was assayed by the Hybritech monoclonal sandwich radioimmunoassay. Results are expressed in IU/l according to the first international reference preparation.

Endoscopic treatment

Before 1988 mainly unipolar electrosurgery was used (Pouly *et al.* 1986). From 1988 on, the technique consisted of a three puncture technique, and used the persufflator (Koninckx & Vandermeersch 1991) to maintain a constant pneumoperitoneum during suction and smoke removal, a CO₂-laser (Sharplan 1060) and a video system.

Following the diagnosis of an ectopic pregnancy blood was aspirated, and the pelvic cavity extensively rinsed (1–2 litres of Ringer's lactate). A careful adhesiolysis was performed to permit free mobilization of the oviduct. By careful inspection, the vascular supply of the ectopic pregnancy in the mesosalpinx was localized and, if located, it was interrupted with diathermy, at

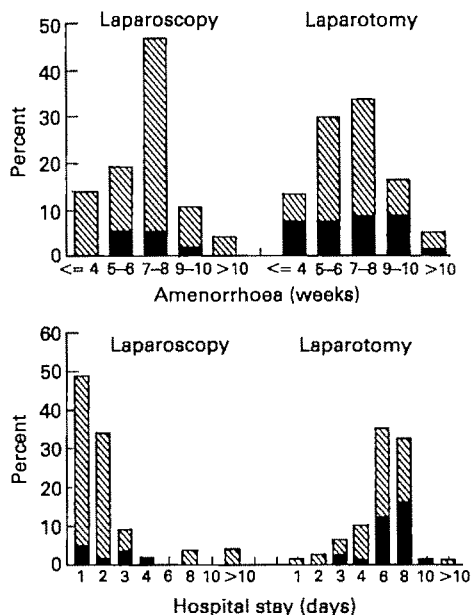


Fig. 1. Duration of amenorrhoea and of hospital stay in women treated with laparotomy or laparoscopy for a ■ ruptured or ▨ unruptured ectopic pregnancy.

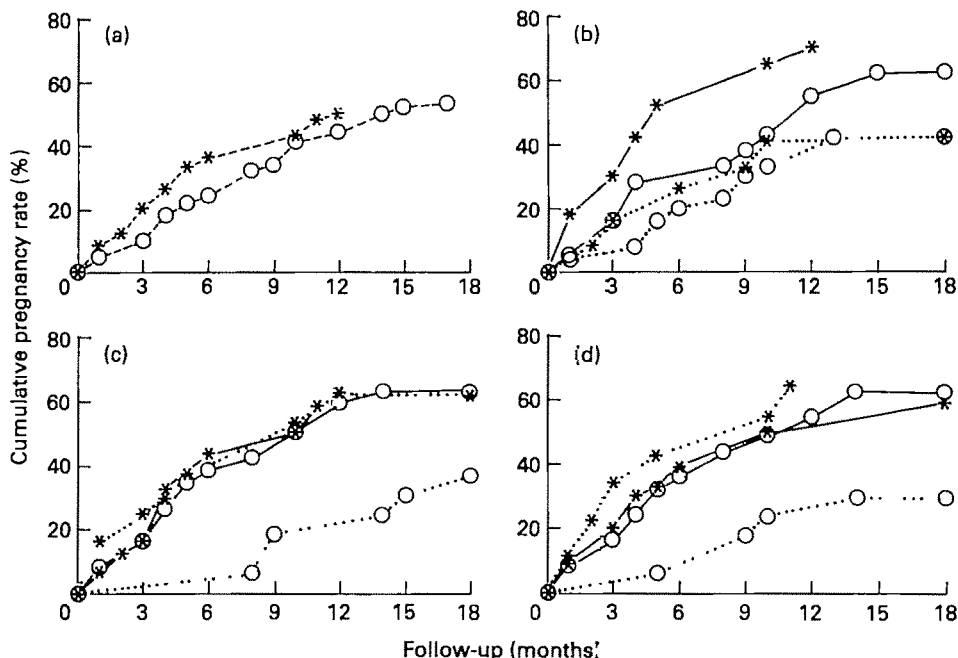


Fig. 2. Cumulative pregnancy rates following an ectopic pregnancy treated with a microsurgeal linear salpingotomy (O) or with CO₂-laser-endoscopy (*). (a) The overall results are depicted, (b) women are grouped into parous (—) and nulliparous (.....); (c) women with (.....) and without (—) a history of infertility and (d) women with (.....) and without (—) a history of PID.

least 0.5 cm from the oviduct. If this could not be done, vasopressin was injected in the mesosalpinx to decrease subsequent bleeding. Using the CO₂-laser, a 1.5 cm longitudinal incision was made in the oviduct; the incision was made slightly lateral of the antimesenteric side, and always placed over the vascular supply, if present. The extra-uterine pregnancy and blood clots were removed with a forceps and/or a suction cannula. If bleeding persisted, after the removal of the ectopic pregnancy vasopressin was injected into the mesosalpinx. Finally the peritoneal cavity was rinsed extensively. The oviductal incision was left open.

Laparotomy

Large ectopic pregnancies with destruction of the oviduct were initially treated by excision, whereas later on, a linear salpingotomy using microsurgical techniques was performed followed by nylon 5-0 suturing in almost all women. Very distal and small ectopics were treated by expression.

Statistics

Statistical calculations used the statistical pack-

age SAS (1985) and differences were tested with the χ^2 and Student's *t*-tests. Analysis of variance (Anova) was used to compare more than two groups, whereas cumulative pregnancy rates were evaluated by life table analysis and Cox multivariate regression (Cox 1972). Means (SD) are indicated unless stated otherwise.

Results

Diagnosis and localization

In unruptured ectopic pregnancies ($n=101$), the diagnosis was made by echography and hCG assays in 67%, by echography only in 22% and by clinical factors only in 11%. In ruptured ectopics ($n=34$) these figures were 38%, 32% and 30% respectively (χ^2 ; $P=0.02$). In the unruptured ectopic pregnancies, the echographic diagnosis was suggestive in 91%, positive in 3%, but false negative in 6%; in the ruptured ectopic pregnancies, no false negatives were encountered. The ectopic pregnancy was localized in the ampulla (50%), at the ampullary isthmus junction (34%), in the ovary (5%) or presented as a tubal miscarriage (10%).

Table 1. Ectopic pregnancies treated with microsurgical linear salpingotomy or CO₂-laser laparoscopy

	Microsurgery (n=42)	CO ₂ -laser laparoscopy (n=34)
Women		
Age (years)	29.7 (4.0)	30.5 (5.2)
Weight (kg)	60.2 (10.8)	60.1 (8.8)
Ectopic pregnancy		
Amenorrhea (weeks)	6.9 (2.1)	7.0 (2.3)
Diameter (cm)	3.2 (1.2)	3.0 (1.4)
% Ruptured	15.3	12.5
Hospital stay (days)*	6.8 (1.6)	2.9 (1.8)
Plasma hCG†		
day 0	866 (317–1918)	1122 (300–3851)
day 3	325 (98–1648)	218 (54–1071)
day 7	84 (19–313)	71 (12–265)
day 14	8 (1–71)	24 (15–78)
day 21	3 (2–5)	12 (2–35)

Results are mean (SD) values unless otherwise stated.

* $P < 0.0001$

† Mean (25–75th centile); day 0 = day of surgery.

Treatments

Of the 135 women, 11 with a tubal miscarriage were treated with pelvic lavage. The 78 laparotomy procedures comprised 55 microsurgical linear salpingotomies, 9 excisions, and 14 salpingectomies. The other 46 laparoscopic treatments used CO₂-laser in 34 and unipolar electrosurgery in 12.

In the randomized 1988–1989 group, women treated by laparoscopy and laparotomy were comparable for age, weight, duration of amenorrhea and diameter of the ectopic pregnancy (Table 1). The duration of hospital stay was much shorter following laparoscopy than after laparotomy ($P < 0.0001$), and was not affected by the diameter or the rupture of the ectopic pregnancy (Table 1, Fig. 1). The postoperative decline of plasma hCG concentrations was comparable in the two groups.

None of the women treated with laparotomy required a second procedure, but in four women (7%) treated with laparoscopy a second (laparoscopic) procedure had to be performed for bleeding in one and for a persisting ectopic pregnancy in the other three. In these women the hCG concentrations (mean, 25th–27th centile) were 956 (353–2591), 169 (52–525), 300 (81–1117), and 533 (216–2377) IU/l before and 3, 7 and 14 days postoperatively.

Pregnancy rates

Analysis was restricted to those women who desired another pregnancy.

In the randomized 1988–1989 group, the overall pregnancy rates (Fig. 2a) were comparable after microsurgical linear salpingotomy ($n=38$) and CO₂-laser-endoscopy ($n=31$). Pregnancy rates were lower ($P=0.004$) in nulliparous women (Fig. 2b). By life table analysis, cumulative pregnancy rates following laparotomy and laparoscopy were comparable in multigravida, in women without a history of infertility and in women without a history of pelvic inflammatory disease (PID) or ectopic pregnancy; cumulative pregnancy rates following laparotomy were lower in women with a history of infertility ($P=0.02$) and slightly but not significantly lower in women with a history of PID or ectopic pregnancy. By multivariate regression (Cox 1972), the cumulative pregnancy rate was significantly ($P=0.009$) higher after CO₂-laser-endoscopic treatment than after microsurgery in nulliparous women with a history of infertility, PID or ectopic pregnancy; in the other women the pregnancy rates were comparable in both groups.

Cumulative pregnancy rates following laparotomy were higher ($P=0.05$) after microsurgical linear salpingotomy ($n=42$) than after excision ($n=10$). During the period 1984 to 1989, cumu-

lative pregnancy rates after 6, 12 and 18 months were 24%, 42% and 51% in the former group and 0%, 10% and 10% in the latter

In the total group the pregnancy following laparoscopic treatment resulted in a further ectopic pregnancy (0%), a miscarriage (6%), and a normal pregnancy (94%). Following laparotomy for ectopic pregnancy these figures were 17%, 18% and 65% respectively ($P=0.026$). For the period 1988–1989 the recurrence rate following microsurgery was only 5%.

Discussion

The feasibility of conservative laparoscopic treatment for ectopic pregnancies is well established. The indications generally have been restricted to smaller (<3 cm), and unruptured ectopic pregnancies without a living fetus. Our data demonstrate that conservative laparoscopic treatment of ectopic pregnancies can safely be extended to women with larger and/or ruptured ectopic pregnancies, provided they are haemodynamically stable.

The most important technical aspects for rapid and safe laparoscopic treatment of ectopic pregnancies in our experience are the following. The persufflator permits flushing the peritoneal cavity with up to 60 litres of CO₂/min (Koninckx & Vandermeersch 1991). This permits continuous suction of blood while maintaining a constant pneumoperitoneum and thus a clear vision. The CO₂-laser is not considered to have major advantages over unipolar electrosurgery for the incision of the oviduct. Ectopic pregnancies are, however, often associated with pelvic adhesions, which limit the mobilization of the oviduct. Our initial failures of laparoscopy, i.e., three women in whom a laparotomy had to be performed because of bleeding, occurred during manipulation when adhesions limited the mobilization of the oviduct and the localization of the bleeding. Therefore, we consider a complete adhesiolysis/salpingolysis mandatory before mobilizing the oviduct. To achieve this rapidly the CO₂-laser is superior to electrosurgery. Coagulation of the irrigating artery is important since in over 50% of women, the subsequent removal of the ectopic pregnancy is completely bloodless. We prefer to limit the injection of vasopressin in the mesosalpinx (Pouly *et al.* 1986) to these women in whom no irrigating artery can be found, or who still bleed after the removal of the ectopic

pregnancy, since with vasopressin we cannot stop the bleeding in all women, necessitating coagulation/endothelium, and since one woman had to have a second operation because of massive bleeding which started more than 12 h after the laparoscopic procedure.

The shorter hospital stay following laparoscopic treatment of ectopic pregnancies is well known (Brumsted *et al.* 1988). There is, however, a higher incidence of incomplete treatment necessitating a repeat intervention in some 7% of women (Henderson 1989; Vermesh *et al.* 1989). Although we consider that these incomplete laparoscopic removals of ectopic pregnancies could be reduced by experience, our 1991 data demonstrate that repeat interventions are still required in some women. A rigorous follow-up by monitoring hCG concentrations is mandatory. An important detail, however, is that in the three women who required a repeat operation hCG concentrations started to rise again after only 1 week of exponential decline, which had been similar to the decline observed in the other women. One should moreover realize that during the second laparoscopic intervention, histologically only necrotic placental tissue and blood clots were found. Therefore one could argue that a repeat intervention might not have been necessary and that a more conservative approach could have been more appropriate (Garcia *et al.* 1987). This needs to be confirmed before it can become clinically applicable.

In the total group postoperative pregnancy rates were comparable with those reported previously (Makinen *et al.* 1989; Mecke *et al.* 1989; Oelsner *et al.* 1987; Pouly *et al.* 1986; Vermesh *et al.* 1989). Although the group treated with excision is small, the significantly lower pregnancy rates suggest that linear salpingotomy should be preferred when possible.

In the 1988–1989 group, which allows a comparison of microsurgical linear salpingotomy and CO₂-laser-laparoscopy, no differences were found in multiparous women and in women without a history of infertility or PID. However, nulliparous women with a history of infertility or PID had a significantly higher pregnancy rate after laparoscopy and this was also true when unruptured ectopic pregnancies only were considered. To explain this, we suggest the following mechanism. The laparoscopy procedure included a complete ovariolysis-salpingolysis to permit good mobilization and visibility but

during microsurgery only a limited adhesiolysis, e.g., not including the other oviduct, was performed, and the differences found could reflect this. Our laparotomy records did not permit us to verify that these women actually had more adhesions. However, we suggest that adhesiolysis during laparoscopic surgery for an ectopic pregnancy may improve the pregnancy rate as well as being necessary for technical reasons.

Reported recurrence rates of an ectopic pregnancy vary between 7 and 30% (Mecke *et al.* 1989; Oelsner *et al.* 1987; Pouly *et al.* 1986). Although our group is small, the observed recurrence rate of <5%, together with our generally low incidence of ectopic pregnancy, could be related to our population, the Leuven area being a small university town, with a low incidence of PID.

In conclusion, our data demonstrate that most women with ectopic pregnancies who are haemodynamically stable can be treated with laparoscopy and that besides the advantages of a lower morbidity, compared with microsurgery the CO₂-laser-endoscopic treatment has a higher postoperative fertility rate in nulliparous women with a history of impaired fertility. It is suggested that this could be explained by the more complete adhesiolysis performed during CO₂-laser-endoscopic treatment.

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The role of *Chlamydia trachomatis* and *Neisseria gonorrhoeae* in the aetiology of ectopic pregnancy in Gabon

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Abstract

Objective—To study the association between ectopic pregnancy and *Chlamydia trachomatis* and *Neisseria gonorrhoeae*.

Design—A prospective observational study with two comparison groups.

Setting—A general hospital in Franceville, Gabon.

Subjects—Forty-five women with ectopic pregnancies and two comparison groups each of 45 women, one at 5 to 12 and the other at 32 to 41 weeks gestation.

Main outcome measures—Serum levels of IgG and IgA antibodies to *C. trachomatis* (L1 and rMOMP) and *N. gonorrhoeae* (pili) in all the women. In the women with ectopic pregnancy peritoneal adhesions were scored and in 40 women samples of tube were cultured for organisms being studied.

Results—IgG and IgA antibodies to *C. trachomatis* (L1) were detected in 84% of the ectopic group and 52 and 39% of the comparison groups ($P < 0.0001$). IgG and IgA antibodies to *N. gonorrhoeae* occurred in 49, 28 and 18% and 49, 28 and 26% of the groups but the differences were not statistically significant. Adhesions were positively associated with the antibodies. *C. trachomatis* was cultured from the tubes of 71% of the women with ectopic pregnancy.

Conclusions—Infection with chlamydia, and probably with *N. gonorrhoeae*, is an important factor in the causation of ectopic pregnancy in Gabon.

Ectopic pregnancy, like tubal infertility, is

generally thought to result from previous tubal infection, usually from sexually transmitted bacteria such as *Neisseria gonorrhoeae* or *Chlamydia trachomatis*. In industrialized countries women who had acute salpingitis had a 7–10 fold risk for ectopic pregnancy (Westrom *et al.* 1981). In Africa also, *C. trachomatis* and *N. gonorrhoeae* are major causes of salpingitis (Piot *et al.* 1983) and both these pathogens are associated with tubal obstruction and infertility.

Gabon, in equatorial Africa, has one of the lowest fertility rates (116/1000 women between 15 and 44 years of age) (Belsey 1976). The main cause seems to be the high prevalence of salpingitis in this area (Muir 1980). Moreover, the average ratio of ectopic pregnancies to live births is 1:62.5, similar to that in Europe. In this paper we present the first prospective study of the role of *C. trachomatis* and *N. gonorrhoeae* in ectopic pregnancy in Africa.

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Subjects and methods

Over a period of 10 months, between May 1988 and February 1989, we studied prospectively 45 of the 56 women who were admitted with an ectopic pregnancy to the general hospital in Franceville, Gabon. Two control groups were formed from women with uncomplicated intra-uterine pregnancies who attended the antenatal clinic. One group included 45 women at 5–12 weeks gestation and the other included 45 women at 32–41 weeks gestation. The women in the control groups were selected when a patient presented with an ectopic pregnancy as the first pregnant woman up to 12 weeks gestation and the first pregnant woman between 32 and 41 weeks gestation attending the routine obstetric clinic. The control groups were selected at these two different gestational ages for three main reasons (i) women in early pregnancy are more likely to be sexually active and have more evidence of sexually transmitted disease (STD) than women in fullterm pregnancy; (ii) early pregnancy cannot be considered as a normal pregnancy since pregnancy loss is not rare in the first trimester; and (iii) little is known about possible variation in chlamydial serology during the course of pregnancy. Controls were matched with the cases for age (within 2 years) and gravidity.

Both cases and controls were drawn from a relatively homogeneous population and were similar in socioeconomic status. All subjects underwent a structured interview in which particular attention was paid to reproductive history, sexual behaviour, contraception and any past evidence of sexually transmitted disease or pelvic infection.

At surgery the appearance of the abdominal cavity was recorded using the classification developed by Mage *et al.* (1987) as follows: stage 1, absent or mild pelvic adhesions; stage 2, moderate pelvic adhesions easily removed during surgery; stage 3, thick pelvic adhesions with a bad fertility prognosis. The fallopian tubes could not be examined laparoscopically. During surgery a sample of fallopian tube with the associated ectopic pregnancy was snipped off into conventional 2SP chlamydial transport medium in 40 of the 45 cases. Specimens were stored in 2SP at -70°C . For culture the swabs were thawed, sonicated, then inoculated by centrifugation onto McCoy cell monolayers in 96-well plates and incubated for 72 h in medium containing 1 $\mu\text{g/ml}$ cycloheximide (Ripa *et al.* 1977).

Chlamydial inclusions were demonstrated by immunoperoxidase using human serum containing known antibodies to *C. trachomatis*.

Cultures from the fallopian tubes were also obtained for *N. gonorrhoeae*. A cotton swab was rotated within the ampulla of the tubes and transported in TGV transport medium (Diagnostic Pasteur, Paris, France). Methods for gonococcal culture were as described by Yvert *et al.* (1984).

A 10 ml sample of venous blood was obtained from each of the 45 women with ectopic pregnancy, but only from 36 and 38 women in the early and late pregnancy control groups respectively. The serum was separated, frozen at -20°C , and transported to Southampton in the UK for measurement of IgG and IgA antibodies to *C. trachomatis* and *N. gonorrhoeae*. Conventional ELISA was performed on duplicate 1/100 dilutions of sera using *C. trachomatis* L1 and *N. gonorrhoeae* P9 pili as antigens (Mabey *et al.* 1985). *C. trachomatis* recombinant 3/4 length outer membrane protein (rMOMP) (Conlan *et al.* 1988), at a concentration of 1 $\mu\text{g/ml}$, was used as a third antigen.

Statistical analysis was performed using the χ^2 test with Yates' correction for small sample sizes.

Results

Over the period of the study, 56 women underwent salpingectomy for ectopic pregnancy and samples were obtained from 45. Table 1 shows the clinical characteristics of the cases and controls. There was no difference between the cases and controls in the frequency of a history of at least one abortion. However, women with ectopic pregnancy had significantly more lifetime partners than controls ($P < 0.001$), and a lower age at first coitus ($P < 0.01$ early pregnancy, $P < 0.05$ late pregnancy) suggesting higher risk sexual behaviour. There was also a more frequent history of pelvic inflammatory disease which, however, was not statistically significant in the small sample available. Neither the cases nor the controls had ever had an intrauterine contraceptive device inserted. The significant association of ectopic pregnancy with increased number of lifetime sexual partners, reduced age at first coitus but not with previous abortion is consistent with the main aetiological factor being sexually transmitted.

At surgery, pelvic adhesions were found in

Table 1. Clinical characteristics of the cases and the two control groups

Clinical characteristics	Cases	Control groups			
	Ectopic pregnancy (n = 45) n (%)	Early pregnancy (n = 45) n (%)	P	Late pregnancy (n = 45) n (%)	P
Age (years)					
Mean (SD)	25.3 (6.5)	25.5 (7.1)	n.s.	25.5 (5.9)	n.s.
Gravidity					
0	3 (6)	3 (6)		4 (9)	
1 to 5	25 (56)	25 (56)	n.s.	23 (51)	n.s.
>5	17 (38)	17 (38)		18 (40)	
History					
Abortion	20 (44)	21 (47)	n.s.	18 (40)	n.s.
Ectopic pregnancy	9 (20)	3 (7)	n.s.	0 (0)	<0.001 (1)
PID	13 (29)	8 (18)	n.s.	6 (13)	n.s.
Lifetime sexual partners					
<5	9 (20)	28 (62)		33 (74)	
5 to 10	10 (22)	8 (18)	<0.001 (2)	5 (11)	<0.001 (3)
>10	26 (58)	4 (9)		7 (15)	
Age at first coitus (years)					
<15	21 (47)	13 (29)	n.s.	11 (25)	<0.01 (4)
>15	24 (53)	32 (72)		34 (75)	

PID = pelvic inflammatory disease.

Significance difference is defined for $P < 0.05$.

(1) $\chi^2 = 10.2$, df = 1, 95% CI 0.083 to 0.317; (2) $\chi^2 = 26.3$, df = 2; (3) $\chi^2 = 31.2$, df = 2; (4) $\chi^2 = 9.4$, df = 1; (5) $\chi^2 = 9.4$, df = 1, 95% CI 0.027 to 0.413.

44% of cases (20/45): 25 (56%) were in stage 1, 16 (35%) were in stage 2 and 4 (9%) were in stage 3.

Plots of the frequency distribution of ELISA results (optical density) for IgG and IgA antibody to *C. trachomatis* L1, rMOMP and *N. gon-*

orrhoeae pili were markedly positively skewed compared with all other populations we have studied (UK, Yugoslavia, Armenia, Gambia), suggestive of a very high overall prevalence of sexually transmitted disease. We have shown previously that at a serum dilution of 1:100 the

Table 2. Prevalence of antibody in the cases and the two control groups

Antibody	Ectopic pregnancy (n = 45) n (%)	Control groups					
		Early pregnancy (n = 36) n (%)	χ^2	P	Late pregnancy (n = 38) n (%)	χ^2	P
IgG							
<i>C. trachomatis</i> L1	38 (84)	19 (53)	8.2	<0.01 (1)	15 (39)	16.2	<0.001 (2)
<i>N. gonorrhoeae</i> pili	22 (49)	10 (28)	3	n.s.	7 (18)	7.1	<0.01 (3)
<i>C. trachomatis</i> rMOMP	34 (76)	21 (58)	2.7	n.s.	15 (39)	11	<0.001 (4)
IgA							
<i>C. trachomatis</i> L1	28 (62)	11 (31)	6.9	<0.01 (5)	11 (29)	7.9	<0.05 (6)
<i>N. gonorrhoeae</i> pili	22 (49)	10 (28)	2.9	n.s.	10 (26)	3.5	n.s.
<i>C. trachomatis</i> rMOMP	10 (22)	11 (31)	0.8	n.s.	12 (32)	1	n.s.

Significance difference is defined for $P < 0.05$.

(1) 95% CI, 0.115 to 0.505; (2) 95% CI, 0.103 to 0.517; (3) 95% CI, 0.262 to 0.638; (4) 95% CI, 0.12 to 0.5; (5) 95% CI, -0.447 to 1.227; (6) 95% CI, 0.123 to 0.532.

Table 3. Surgical findings and the results of fallopian tubes culture and serology

	<i>C. trachomatis</i> antibodies						<i>N. gonorrhoeae</i> antibodies					
	IgG			IgA			IgG			IgA		
	Negative	Positive	P	Negative	Positive	P	Negative	Positive	P	Negative	Positive	P
Pelvic adhesions												
(n = 45)												
Presence	0	26 (68)	<0.01	8 (47)	18 (64)	n.s.	11 (48)	15 (68)	n.s.	14 (61)	12 (26)	n.s.
Absence	7 (100)	12 (32)	(1)	9 (53)	10 (36)		12 (52)	7 (32)		9 (39)	10 (19)	
Culture of Fallopian tubes												
(n = 40)												
Positive	5 (71)	20 (60)	n.s.	6 (43)	19 (73)	<0.01	0 (0)	0 (0)		0 (0)	0 (0)	n.s.
Negative	2 (29)	13 (40)		8 (57)	7 (27)	(2)	0 (0)	0 (0)		0 (0)	0 (0)	

Data are shown as n (%). Statistical significance is defined for $P < 0.05$, (1) $\chi^2 = 10.4$, df = 1, 95% CI 0.532 to 0.828, (2) $\chi^2 = 10.4$, df = 1, 95% CI -0.61 to 0.01.

optical density is linearly related to titre on end-point dilution (Mabey *et al.* 1985). On the basis of these frequency distributions we assigned arbitrary 'cut-off' values for the optical density of positive sera of >0.7 or IgG antibody to whole *C. trachomatis* L1 or to gonococcal pili; >0.45 for IgG antibody to rMOMP, >0.2 for IgA antibody to rMOMP and >0.3 for IgA antibody to *Chlamydia* and gonococci.

Justification for these cut-off values for IgG antibody to *Chlamydia* was the observation that only sera with an optical density ≥ 0.7 to whole *Chlamydia* had an optical density to rMOMP of >0.45 . Similarly for IgA only sera with an optical density of >0.3 to whole *Chlamydia* had an antibody level to rMOMP of >0.2 . For positive sera there was good agreement for antibody levels to the two chlamydial antigens ($P < 0.0001$).

The prevalence of antibody among women with ectopic or intrauterine pregnancy is shown in Table 2. Among women with ectopic pregnancy, 84% (38/45) were positive for antibody to whole *Chlamydia* and 76% (34/45) were positive for antibody to rMOMP. Comparable figures in the early pregnancy controls were 53% and 58% for *Chlamydia* and rMOMP, and in the late pregnancy controls 39% for both antigens. Some 49% (22/45) of women with ectopic pregnancy had IgG antibody to gonococcal pili compared with 28% of the early pregnancy control women and 18% of those with full-term pregnancy. From these data it may be seen that women with ectopic pregnancy had significantly more antibody to both chlamydial antigens than did the control women in early or late pregnancy

($P < 0.005$). Likewise there was a higher prevalence of antibody to gonococcal pili in the ectopic pregnancy group, but this was only statistically significant when compared with the control women in late pregnancy ($P = 0.007$).

Of the 45 women with ectopic pregnancy 62% had circulating IgA antibody to *C. trachomatis* compared with 31% and 29% in the early and late pregnancy control groups. Furthermore, 49% of the ectopic pregnancy group had IgA antibody to *N. gonorrhoeae* pili compared with 28% and 26% in the early and late pregnancy control groups. Although the trend is the same, these differences were not statistically significant due to small sample size.

In all the ectopic pregnancy groups except one, high IgA levels were associated with high levels of IgG, for both pathogens. *C. trachomatis* was cultured from the fallopian tubes of 25 of 40 cases of ectopic pregnancy (62%). *N. gonorrhoeae* was not isolated from this site. Thus, unlike Southampton (Robertson *et al.* 1988), many Gabonese women with ectopic pregnancy were currently infected with chlamydiae, probably explaining why there was such a high prevalence of IgA antibody, which is a relatively short duration antibody.

Table 3 shows the relation between gross surgical findings and the results of chlamydial fallopian tube culture and serology. The positive predictive value (PPV) and negative predictive value (NPV) of chlamydial IgA serology for culture of the fallopian tubes for *C. trachomatis* were 0.73 and 0.57, respectively. Chlamydial IgG serology had a PPV of 0.6 and a NPV of 0.29 for culture of the fallopian tubes for *C. trachomatis*.

High levels of IgG to *C. trachomatis* are highly associated with the presence of pelvic adhesions.

Discussion

Tubal infection has been considered the main cause of infertility and ectopic pregnancy in Africa (Belsey 1976; Ville *et al.* 1991; Retel-Laurentin 1974) although direct evidence for the latter has not been obtained hitherto. The hypothesis that sexually transmitted disease is significantly associated with ectopic pregnancy was supported by the observation that women with ectopic pregnancy had higher risk sexual behaviour than women with intrauterine pregnancy. Moreover, the greater prevalence of chlamydial and gonococcal antibodies in women with ectopic rather than intrauterine pregnancy strongly supports the hypothesis, as serum IgG antibodies represent the cumulative history of the individual's exposure to infection. The reliability of the serological methods we used has been reviewed recently (Robertson *et al.* 1988). Antibodies to *C. psittaci* and *C. pneumonia* may cross react with the *C. trachomatis* antigen used, while antibody to meningococcal infection may cross react with gonococcal pili. However, there is no reason to suppose that any of the study population groups were heterogeneous in respect of their exposure to these cross reactive pathogens. It is reasonable to conclude that sexually transmitted disease is a major, if not dominant, factor in the aetiology of ectopic pregnancy in Gabon.

Gonococcal infections have been associated with pelvic inflammatory disease and its tubal sequelae in Africa (Muir *et al.* 1980), although in a study of infertility due to tubal occlusion in the Gambia, West Africa, *Chlamydia* appeared to be more important (Mabey *et al.* 1985). Our failure to isolate gonococci from the fallopian tubes was probably related to technical problems associated with the transport of specimen as IgA antibody to *N. gonorrhoeae* pili was almost twice as common in women with ectopic rather than intrauterine pregnancy. In Gabon there is a strong association between chlamydial infection, acute salpingitis and tubal infertility (Reniers *et al.* 1989; Frost *et al.* 1987). In many industrialized countries, *C. trachomatis* rather than *N. gonorrhoeae* appears to be the main pathogen associated with tubal infertility (Conway *et al.* 1984; Anaestad *et al.* 1987; Sellors *et al.* 1988) and ectopic pregnancy (Svensson *et al.*

1985; Brunham *et al.* 1986; Hartford *et al.* 1987; Dubuisson *et al.* 1987; Walters *et al.* 1988; Robertson *et al.* 1988; Diquelou *et al.* 1988). In Gabon (Leclerc *et al.* 1988) the prevalence of *C. trachomatis* infection is much higher than in industrialized countries. It is not surprising, therefore, that our serological studies indicated a strong association between ectopic pregnancy and chlamydial and gonococcal infections, with chlamydia the more important of the two pathogens. The results confirm the importance of *C. trachomatis* in STD in Africa.

One surprising finding was the fact that 62% of Gabonese women with ectopic pregnancy still had active tubal chlamydial infection. This is the highest rate of current chlamydial infection reported for ectopic pregnancy; most authors found negative tubal cultures (Brunham *et al.* 1986; Hartford *et al.* 1987; Diquelou *et al.* 1988) although there was one report of a 31% prevalence of active infection (Bentsi *et al.* 1985). We assume that in industrialized countries, ectopic pregnancy probably occurred in women with past, rather than current, chlamydial infection. The much greater frequency of active chlamydial infection in ectopic pregnancy in Gabon is probably explained by the markedly higher prevalence of chlamydial infection (Leclerc *et al.* 1988).

The fact that a history of pelvic inflammatory disease was uncommon in women with antichlamydial antibodies has been noted by others (Brunham *et al.* 1986; Hartford *et al.* 1987; Walters *et al.* 1988) and supports the view that *C. trachomatis* salpingitis is more likely to be subclinical (Sellors *et al.* 1988; Patton *et al.* 1989; Rosenfeld *et al.* 1983) than salpingitis due to other pathogens. Clearly many women are unaware that they have a tubal infection and therefore do not seek treatment. The correlation between chlamydial antibodies and the severity of pelvic lesions at the time of surgery provides additional evidence for the crucial role of *C. trachomatis* in tubal disease (Table 3), although tubal chlamydial infection is not invariably associated with damaged tubes (Menchaca *et al.* 1988).

The question arises whether IgA antibodies are useful for the diagnosis of upper genital tract chlamydial infection in women. In our study antichlamydial IgA antibodies were very prevalent and were associated with active infection of the fallopian tubes. This association was not found for IgG serology, suggesting that IgA anti-

bodies are associated with recent or current chlamydial infection. Furthermore we clearly show that high levels of IgG to *C. trachomatis* are associated with pelvic adhesions, reflecting passed infection (Table 3). This is supported by the frequent isolation of chlamydiae from the fallopian tubes. Robertson *et al.* (1988) found a low prevalence of antichlamydial IgA in women with ectopic pregnancy in Southampton. However, in this population only one patient's fallopian tube was positive for chlamydial antigen. A high prevalence rate of specific elevated IgA correlated with positive *C. trachomatis* isolation has been found in non-gonococcal urethritis (Cevenini *et al.* 1984), in patients seeking abortion (Csango *et al.* 1988), in salpingitis (Piura *et al.* 1985), in epididymitis (Kaneti *et al.* 1988) and in women with obstructive infertility (Sarav *et al.* 1988). In our study, IgA antichlamydial antibodies reflected active infection of the fallopian tubes in Gabonese women with ectopic pregnancy, with higher predictive values than for IgG.

In developing countries such as Gabon, where methods for the laboratory isolation of *Chlamydia* are not generally available yet there is a substantial probability that ectopic pregnancy may be associated with current chlamydial infection, high serum IgA levels may provide a useful guide to clinician, with positive predictive values of 0.73 and 0.57 respectively. This is unlikely to be the case in developed countries, where the prevalence of active chlamydial infection in ectopic pregnancy appears much lower (Robertson *et al.* 1988) and more reliable diagnostic tests are generally available. A particular difficulty is the patient whose lower genital tract infection has resolved, invalidating most of the laboratory diagnostic tests, but in whom infection is still present in the upper genital tract. In such patients our strategy would be to attempt chlamydial isolation with a sleeved swab from the endometrium, where chlamydial infection is often associated with plasma cell endometritis. On fundamental immunological principles (Allardye & Bienenstock 1984) we would expect upper genital tract infection to activate the common mucosal immune system. This would result in the appearance of specific sIgA antibody at the cervix, either as a result of direct drainage from the endometrium, which is the main source of lower genital tract antibody (Parr & Parr 1988) or as a result of cervical colonization with circulating sIgA plasmablasts (Allardye & Bienenstock 1984). sIgA antibody

is much shorter lived than serum IgA and is thus far more likely to be associated with current infection. At present we consider it premature to use IgA based tests for the diagnosis of upper genital tract infection with STD agents until the technology is substantially improved. Such a test has to be specific for both the pathogen and for secretory not circulating IgA, as well as being adequately sensitive to measure the low levels of sIgA present in cervical secretion. In this respect we have recently been encouraged by observing a strong positive correlation between culture positive chlamydial cervicitis and the presence of antichlamydial sIgA antibody detected by a highly sensitive, redox-amplified ELISA in the supernatant transport medium of chlamydial culture swabs (data in preparation). We are currently investigating how long these antibodies persist following antichlamydial therapy, and whether similar tell-tale antibodies are produced following upper genital tract infections.

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An audit of the management of ectopic pregnancy

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Abstract

Objective—To estimate the local incidence of ectopic pregnancy and to review the management of ectopic pregnancy with reference to those misdiagnosed at presentation. To establish management guidelines to be applied to all possible ectopic pregnancies.

Design—A review of all ectopic pregnancies presenting over a 2-year period, and of emergency gynaecological admissions during 4 months.

Setting—A teaching hospital

Results—The local rate of ectopic pregnancy was similar to that seen in other UK studies. Nineteen (13%) women with ectopic pregnancies were sent home with an incorrect diagnosis. Eight were recalled but eight required emergency admission and one died at home. Undue confidence in ultrasound reports and failure to follow up inconclusive histology results were a feature in cases where patients were not recalled. A set of simple management guidelines has been drawn up. Amongst general gynaecological admissions 1 in 12 of all first trimester complications was an ectopic pregnancy. Amongst apparently true uterine miscarriages 20% of histological examinations were inconclusive and histology and ultrasound examinations failed to confirm a uterine miscarriage in 14% of apparently true missed miscarriages.

Conclusions—Ectopic pregnancy is common amongst first trimester complications. Adherence to simple management guidelines would minimize the number of patients requiring emergency admission, though up to 20% of patients with apparently true uterine miscarriages would also require further investigation.

A review of the management of women with an ectopic pregnancy over a 2-year period was undertaken. The aims of the audit were three-fold. (i) To establish the rate of ectopic pregnancy in the district population and within the emergency gynaecological intake with a complication of the first trimester. (ii) To establish the proportion of women with a final diagnosis of ectopic pregnancy who were initially discharged with an incorrect diagnosis and to identify factors contributing to the error, thus enabling guidelines to be established for all gynaecologi-

cal emergencies. (iii) To apply these guidelines to a review of the management of a sample of the gynaecological intake with first trimester complications.

Subjects and methods

A retrospective study was undertaken at the Princess Anne Hospital, Southampton, which included all women with a final diagnosis of ectopic pregnancy who presented between February 1 1988 and January 31 1990. The hospital is the major gynaecological unit in the Southampton and South-West Hampshire Health District and the only one to accept gynaecological emergencies. Cases were identified by examination of the theatre and hospital records and a critical analysis of the case records was undertaken. Review

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of instances where the diagnosis was missed enabled the construction of a set of management recommendations for use where ectopic pregnancy was a possible diagnosis.

In addition, the notes of women with a possible diagnosis of ectopic pregnancy admitted during February, June, September and December 1988 were reviewed. Women undergoing elective procedures, readmitted following complications of elective procedures, outside the age range 15–44 years, with pregnancies advanced more than 14 weeks or who were known or suspected to be pregnant but where the possibility of ectopic pregnancy was not an issue were excluded from the study. The remainder were therefore women either with a complication of the first trimester or in whom pregnancy could not be immediately excluded. This sample of admissions allowed an estimation of the emergency admission population at risk of ectopic pregnancy, subsequently used as denominator in the estimations of hospital based rates. Records were classified by the diagnosis at discharge and also on the basis of the guidelines established for the management of ectopic pregnancy.

Results

Local population projections estimated the female population aged 15–44 years to be 88 105. During 1988, 5812 women resident in the District were delivered and 1113 had a termination of pregnancy (Wessex RHA, 1989; OPCS, 1989).

Ectopic pregnancies

During the two-year study period 149 ectopic pregnancies were treated. Theatre records in the two other NHS hospitals in the district which undertook emergency surgery revealed no cases of ectopic pregnancy. The notes relating to two patients could not be located.

Because an infertility/IVF unit is based in Southampton eight women, resident outside the district were admitted with ectopic pregnancies following local IVF or infertility treatment. Similarly three women resident within the district had an ectopic pregnancy following embryo transfer. These cases serve to inflate the local rate of ectopic pregnancies and they have been omitted when comparing local rates with figures from other studies, though they have been

included in the analysis of hospital based data. Fifteen women with ectopic pregnancies who were not receiving IVF or infertility treatment who were resident outside the area have been included in calculations on the assumption that cases imported are balanced by women resident in the district but presenting elsewhere.

Of the 147 women with ectopic pregnancies, for whom details were available, 31 (21%) were treated without delay because of their clinical condition or because the clinical evidence was so strong that investigations were unnecessary. Of the remaining 116 women 105 were investigated by abdominal ultrasound scans, urinary or serum β -hCG assays, or both, before surgery or evacuation of the uterus.

Of this group of 105 women, 8 (8%) (representing 5% of all ectopic pregnancies) had been allowed home with diagnoses other than ectopic pregnancy but were recalled when either follow-up pregnancy tests suggested a continuing pregnancy or the histological examination of tissue gathered at uterine evacuation did not confirm a uterine miscarriage. However, 11 women (10%) (representing 7% of all ectopic pregnancies) were discharged either with the wrong diagnosis and no arrangements for follow up, or were allowed home pending investigations unavailable during their admission. Of these 11 women, two returned for investigation and were diagnosed and treated, eight were readmitted as emergencies (not recalled), two being readmitted twice. One woman died at home.

Table 1 summarizes clinical events in these 11 women who were either not recalled or allowed home pending investigation, and the errors made in management are classified in Table 2. The time taken for histological analysis of evacuated tissue to become available and the interval between evacuation and readmission is shown in Table 3.

Review of cases allowed the following simple set of recommendations to be made.

1. Tissue should always be sent for histological examination.
2. When histological examination of the tissue obtained at uterine evacuation does not confirm the presence of a uterine miscarriage the patient should be recalled.
3. The diagnosis of missed miscarriage on ultrasound scan where the fetus is not seen should be treated with caution.
4. There should be rapid return of histology results.

Table 1. Course of events in 11 women with ectopic pregnancies who were misdiagnosed or sent home pending investigation

No.	(Adm)	LMP (days)	Investigations	Diagnosis	Action	Histology
1	(1)	39	sβhCG=+; U/S=No fetus seen 25 mm gestation sac	Threatened miscarriage	Observe Discharge	—
2	(2)	51	U/S=pelvic mass	Ectopic pregnancy	Laparotomy	—
	(1)	38	sβhCG=+; U/S=uterine sac and ovarian cysts	Pain ?cause settled	Observe Discharge	
	(2)	40	U/S=tiny sac ?Ovarian cyst Free pelvic fluid	Pain ?cause settled	Observe Discharge	
3	(3)	56	uhCG=+; U/S=pelvic mass	Ectopic pregnancy	Laparotomy	—
	(1)	42	uhCG(home)=+; U/S=Uterine preg. CRL=10 mm. No heart seen. Mishapen sac	?Viable ?Missed miscarriage	Review in one week	—
	(2)	49	U/S='missed abortion'	Missed miscarriage	ERPOC	No villi seen
4	(3)	54	uhCG=+; U/S=pelvic mass	Ectopic pregnancy	Laparotomy	—
	(1)	46	uhCG(home)=+	Probable miscarriage	ERPOC 'POC seen'	No villi seen*
	(2)	91	sβhCG=+	Ectopic pregnancy	Laparotomy	—
5	(1)	?†	uhCG(home)=+, U/S=?POC	Incomplete miscarriage	ERPOC	Arias-Stella change
	(2)	+11	sβhCG=+	Ectopic pregnancy	Laparotomy	—
6	(1)	46	U/S='complete miscarriage'	Miscarriage	ERPOC	Decidua No villi seen
	(2)	64	sβhCG=+	Ectopic pregnancy	Laparotomy	—
7	(1)	45	uhCG(home)=+, U/S=IUCD with ?POC/endometrium	Incomplete miscarriage	ERPOC	Arias-Stella change No villi seen
	(2)	54	sβhCG=+	Ectopic pregnancy	Laparotomy	—
8	(1)	73	uhCG=+; U/S=empty uterus	Incomplete miscarriage	ERPOC	Nil to support pregnancy
	(2)	103	Died at home from ruptured ectopic pregnancy			
9	(1)	64	uhCG(home)=+	Incomplete miscarriage	ERPOC	No histology sent
	(2)	70	U/S=ectopic pregnancy	Ectopic pregnancy	Laparotomy	—
10	(1)	55	sβhCG=+;	?	Home; review	—
	(2)	57	U/S=?degenerating sac	Ectopic pregnancy	Laparotomy	—
11	(1)	<30	None	?	Home, review	—
	(2)	<32	sβhCG=+; U/S=pelvic mass	Ectopic pregnancy	Laparotomy	—

*General practitioner contacted but no action apparent until seen 6 weeks later in the gynaecology clinic

†Patient was 4 months postpartum, regular menstruation not established.

Abbreviations: POC, products of conception; ERPOC, evacuation of retained POC; hCG, human chorionic gonadotrophin, sβhCG, serum beta hCG; uhCG, urinary hCG; U/S, ultrasound scan; LMP, last menstrual period

Table 2. Classification of case histories

Patient no.	Errors
1-3, 6	Undue confidence placed in the result of an early abdominal ultrasound scan.
3-8	Undue confidence placed in the macroscopic appearance of tissue removed at uterine evacuation. No recall arranged where histological examination of evacuated tissue did not confirm the presence of a uterine miscarriage.
9	No histology specimen sent from theatre.
10-11	Allowed home pending further investigation

General gynaecological emergency admissions

A total of 449 women satisfying the criteria outlined earlier were admitted as gynaecological emergencies during the four sample months of 1988. The case notes of 11 (2.4%) could not be located. The notes of the remaining 438 patients were reviewed and classified by the diagnosis given (or implied) at discharge, again assuming miscarriages in women not resident locally are balanced by a similar number of local women presenting elsewhere.

Five women (1.1%) took their own discharge before diagnosis and one woman underwent uterine evacuation on the basis of a clinical diagnosis of missed miscarriage.

Miscarriage (bleeding and pain in a pregnant woman leading to miscarriage). Overall 159 women received this diagnosis (36% of admissions, 52% of admissions where the diagnosis was a first trimester complication). In 28% management did not satisfy the recommendations listed above. No tissue for histological examination was sent in 12 (8%) and no histology report was received in two (1%). Histological examination did not confirm the presence of an intrauterine pregnancy (chorionic villi seen) in 30 (19%) and there was no evidence of follow-up

Missed miscarriage (missed miscarriage or blighted ovum diagnosed on abdominal ultrasound scan). Forty-three women received this diagnosis (10% of admissions and 15% of patients with a first trimester complication). In 14% no fetal pole was seen and tissue was either not sent for examination or did not confirm the presence of an intrauterine pregnancy

Ectopic pregnancy. Twenty-six women

received this diagnosis (6% of admissions, 9% of patients with first trimester complications).

The remaining admissions were women with threatened miscarriage (12%), with living intrauterine pregnancies and pain (4%) and with pelvic pain who were not pregnant (31%).

During the four index months 42 laparoscopies were carried out for suspected ectopic pregnancy of which 26 (62%) were positive.

Discussion

This study shows that ectopic pregnancy is a common condition (Table 4). The incidence is higher than that derived in other UK studies, but does not approach those found in the USA and Finland.

Variations in rates in the UK may reflect different population structures, different contraceptive practices, earlier diagnosis of tubal pregnancy, some of which might otherwise have miscarried spontaneously, or a genuine difference in the incidence of ectopic pregnancy.

The study suggests that women in the reproductive age range admitted as emergencies with a complication of the first trimester or with symptoms suggesting ectopic pregnancy have a 1 in 18 chance of carrying an ectopic pregnancy, a risk that rises to 1 in 12 if pregnancy is confirmed.

The review of the clinical course of the 11 ectopic pregnancies given an incorrect diagnosis initially, or sent home pending investigations, allows a set of recommendations to be drawn up. These are not controversial nor do they promote new practices in the management of suspected ectopic pregnancy. However, when the recommendations were applied retrospectively to the group of women admitted as emergencies who received the (assumed correct) diagnosis of uterine miscarriage the study shows that the management of a significant number fell short of the

Table 3. Admission-readmission interval and time to receive histological reports

Patient no.	Interval between excavation and	
	Issue of histology report (days)	Readmission (days)
3	6	7
4	5	45
5	4	11
6	8	18
7	6	7
8	7	—

Table 4. Comparison of ectopic pregnancy rates

	Present study	Scottish data ¹ (1988)	Aberdeen study ² (1980-84)	Finnish study ³ (1984)	U.S. data ⁴ (1987)
Rate per 1000					
Maternities	11.9	9.2	8.7	27.3	23.1
Pregnancies*	9.1	7.3	6.4	21.4	16.8
Pregnancies**	8.7	6.8	—	—	—
Women, aged 15-44	0.78	0.54	0.45	—	1.53

¹Information and Statistics Division, Scottish Health Service (Personal communication)

²Flett *et al.* (1988).

³Hemminki & Heinonen (1987).

⁴Anonymous (1990)

*Based on admissions for miscarriages and induced abortions plus total births.

**Based on total births and therapeutic abortions plus estimated miscarriage rate (12%, Regan *et al.* 1989).

recommendations. In particular, in almost 20% of those in whom the diagnosis of miscarriage was made, evacuated tissue did not confirm the presence of a uterine miscarriage yet no steps were taken to follow up the patient. In some cases the miscarriage may have been obvious (e.g., fetal parts seen) but this was rarely the case. Failure to follow up unsatisfactory histological reports was a feature in six of nine misdiagnosed ectopic pregnancies reviewed in this study. Endometrial biopsy in ectopic pregnancy can show a wide range of histological types (Ollendorf *et al.* 1987) and only the presence of trophoblastic tissue confirms the presence of an intrauterine pregnancy. The picture is further complicated by heterotopic pregnancies, and by the likelihood that some with inconclusive histological reports are true ectopic pregnancies which will subsequently resolve spontaneously. High rates of spontaneous resolution have been observed (Fernandez *et al.* 1988).

In patient 3 (Table 1) initial abdominal ultrasound scans suggested an intrauterine fetal pole, raising the possibility of a heterotopic gestation. However, subsequent histological examination of evacuated tissue did not support this possibility.

In 14% of patients with a missed miscarriage or blighted ovum the abdominal ultrasound scan was consistent with a failed intrauterine pregnancy, but no fetus was seen and no histological confirmation was obtained. Abdominal ultrasound scans in early pregnancy can be difficult to interpret (Jain *et al.* 1988) and undue faith in such scans was a feature in four of the nine patients who were diagnosed.

In such circumstances the patient should be

recalled and further investigated. This is not a recommendation for mandatory laparoscopy which has its own morbidity. Based on this study, 108 patients who had miscarried would be recalled each year because the presence of an intrauterine miscarriage had not been confirmed. Repeat ultrasound examinations (ideally vaginal), pregnancy testing and clinical examination would clarify the diagnosis.

Two women with ectopic pregnancies were sent home with investigation deferred because ultrasound facilities were not available at the weekend. It is difficult to comment on such decisions made on clinical grounds. However, the diagnosis was made quickly when they returned and it seems likely that they would have been treated immediately if facilities had been available in the first instance. As there is often considerable pressure on junior staff to discharge women in whom symptoms have abated, investigations should be available at weekends and holidays.

Table 3 illustrates that re-admission may be required only a few days after discharge. Streamlining the system by which histology reports are issued and establishing a system whereby each is reviewed early and the patient recalled should be an effective measure.

There can be few obstetricians and gynaecologists who have not at some time misdiagnosed an ectopic pregnancy. Vaginal ultrasound scanning may make the diagnosis of this condition easier but this is not universally available. Women with pelvic pain, vaginal bleeding and amenorrhea form the bulk of emergency admissions and clinical judgement is relied on heavily when deciding which patient with the

apparent intrauterine miscarriage may be carrying a tubal pregnancy. Moreover, incomplete and missed miscarriage are such common events that their management often falls to the most junior member of the emergency team.

The study suggests that about 20% of women with ectopic pregnancies presenting to the hospital undergo laparoscopy/laparotomy as the primary diagnostic procedure. Of the remainder about 10% are misdiagnosed and may require emergency admission later. This figure could be reduced by the adoption of simple recommendations in the management of all gynaecological emergency admissions. Inevitably this would lead to further investigation of women who have had a genuine intrauterine miscarriage, but this need not necessarily involve surgery.

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Colposcopically directed punch biopsy: a potentially misleading investigation

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Abstract

Objective—To determine the relation between the histology of an initial colposcopically directed punch biopsy and a subsequent diathermy loop excision biopsy of the transformation zone, and the effect of lesion size on this relation.

Design—Prospective observational study of loop diathermy excision biopsies of the cervical transformation zone.

Setting—Academic unit colposcopy clinics at The Birmingham and Midland Hospital for Women and Dudley Road Hospital, Birmingham.

Subjects—243 women managed by colposcopy and directed punch biopsy followed by loop diathermy excision.

Outcome measures—The histology of the punch biopsy and the excised transformation zone and the size of the abnormal lesion.

Results—In 132 (54%) of the 243 women the histology of the punch biopsy and loop excision specimen did not agree. In 62 (47%) of these 132 women a more severe lesion was found in the excised transformation zone, including three unsuspected adenocarcinoma *in situ* and one stage Ia1 cancer. In 39 (41%) of the 96 women in whom a lesion of CIN 3, or greater severity, was found in the loop excision specimen, the paired punch biopsy had suggested a lesion of lesser severity. In small area lesions, the punch biopsy was more likely to show more severe disease than the loop excision specimen ($P = 0.0014$).

Conclusions—The results suggest that directed punch biopsy is an inadequate endpoint by which to judge the severity of an epithelial lesion. The findings have important implications for patient management and the design of trials and cast doubt on the results of studies using punch biopsy as an endpoint.

The assessment of women presenting with abnormal cervical cytology and the selection of those who are suitable for local ablative treatment relies on colposcopic assessment of the cervical transformation zone and histological

appraisal of a directed punch biopsy. Fundamental to such a management strategy is the assumption that the colposcopist can identify accurately the area of most severe epithelial abnormality from which to take a punch biopsy. The ability of the colposcopist to determine accurately the severity of intraepithelial lesions and even to diagnose early invasion has been questioned (Benedet *et al.* 1985). This must lead the clinician to doubt the validity of a histological diagnosis which rests solely on a colposcopically directed punch biopsy, particularly because of reports of invasive disease after local destructive treatment (Jordan *et al.* 1985; Ali *et al.* 1986).

In the past, assessment of the relation between the histology determined by punch

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biopsy and the actual histology of a lesion has only been possible when a cone biopsy has been performed. Such cases are highly selected, representing a population of women with lesions unsuitable for local destruction, and may not give a true reflection of the accuracy of punch biopsy in the management of women with an abnormal smear. Diathermy loop excision of the transformation zone as an alternative to local destruction has provided an opportunity to assess again the use of punch biopsy in the management of women with abnormal cytology. We have analysed data on patients managed by colposcopy and directed punch biopsy, followed by diathermy loop excision of the transformation zone, in order to determine the relation between the histology of the initial directed biopsy and the histology in the excised transformation zone. We also assessed the influence of lesion size, as judged by the colposcopist, on this correlation.

Patients and methods

Since 1988, women with abnormal cytology attending the academic unit colposcopy clinics at the Birmingham and Midland Hospital for Women and the Dudley Road Hospital have been treated by loop diathermy excision of the transformation zone if an epithelial abnormality suitable for local destruction is diagnosed. All patients with cytological or colposcopic features suggestive of invasive carcinoma were excluded from this programme of management. During the introductory phase of this programme 243 women were managed by initial directed punch biopsy, to establish the diagnosis, followed by excision of the transformation zone at a subsequent clinic attendance (the median interval between directed punch biopsy and transformation zone excision was 8 weeks (range 6–14)). Thus, 243 paired punch biopsy and loop excision biopsy specimens were obtained. The findings in these paired biopsies form the basis of this report.

Initial colposcopic assessment was made by trained colposcopists using a standard assessment protocol comprising application of 5% aqueous acetic acid followed by punch biopsy from the site of the worst apparent epithelial abnormality identified. An assessment of the size of the lesion was made by the colposcopist at the initial assessment. This was achieved by applying a grid to the image of the cervix creat-

ing eight sectors (four inner and four outer) permitting the size of the whole lesion to be expressed by the number of sectors involved (Fig 1). At a subsequent clinic attendance women considered suitable for local destructive treatment were treated by diathermy loop excision biopsy of the transformation zone. The procedure was performed under local analgesia after repeat colposcopic assessment. Analgesia was obtained by infiltration of up to three 2 ml ampoules of 2% Citanest (prilocaine and fely pressin, Astra).

The biopsy obtained was fixed immediately in Bouin's fixative and subsequently cut into sequential blocks and examined according to a standard protocol similar to that used for the examination of cold knife cone biopsy specimens in our laboratory. A mean of eight blocks per specimen were obtained.

Data were recorded prospectively on proformas and stored on computer at the Academic Department of Obstetrics and Gynaecology of the University of Birmingham.

Results

In all of the punch biopsy specimens it was possible to make an assessment regarding the presence or absence of dysplastic epithelium but in two cases the pathologist found it difficult to grade the lesion accurately. Heat artifact was noted in 19 of the loop excision specimens but it did not interfere with histological interpretation. In a further six loop excision specimens heat arti-

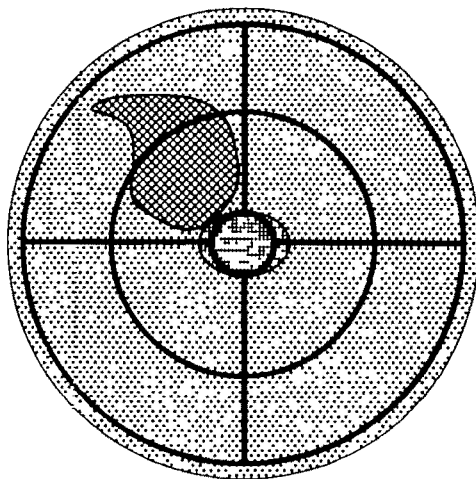


Fig. 1. Grid used for assessment of lesion size. ○, cervix; ■, endocervical canal; ■, lesion; —, grid.

Table 1. Histology of punch and loop biopsies in 243 women with abnormal cervical cytology

Loop biopsy results	Punch biopsy results				
	NAD/ HPV	CIN 1	CIN 2	CIN 3	Total
NAD/HPV	26	20	21	9	76
CIN 1	5	17	8	3	33
CIN 2	10	8	11	9	38
CIN 3	9	10	16	57	92
Invasive	0	0	0	1	1
AIS	0	0	2	1	3
Total	50	55	58	80	243

Abbreviations NAD, no epithelial abnormality detected; HPV, evidence of human papilloma virus infection alone, CIN, cervical intraepithelial neoplasia; AIS, adenocarcinoma in situ.

fact was judged by the pathologist to have affected interpretation significantly.

The results of histological examination of the biopsy specimens and the comparison between punch biopsy and loop excision biopsy results are shown in Table 1. In 132 (54%) of the 243 women the results of the punch biopsy did not agree with those of the subsequent loop excision specimen. In 70 (53%) of the women where there was disagreement the severity of abnormality found in the punch biopsy was greater than that in the loop excision specimen. Of more concern were the 62 (47%) women where a more severe lesion was found in the excised transformation zone including three unsuspected adenocarcinomas in situ (AIS) and one stage Ia1 invasive squamous cervical cancer. In 39 (41%) of the 96 women in whom a high grade lesion (CIN 3, invasive carcinoma or AIS) was found in the loop excision specimen the

paired punch biopsy specimen had suggested that the lesion was of lesser severity. In 25 of these 39 women (24 CIN 3 and 1 AIS) the whole lesion occupied no more than four sectors. In the remaining 15 (11 CIN 3, 1 stage Ia1 and 2 AIS) the whole lesion occupied five or more sectors.

The likelihood of discrepancy between the punch biopsy and the loop excision biopsy appeared to be related to the overall size of the lesion as assessed by the colposcopist (Table 2). The punch biopsy was more likely to indicate a higher grade of lesion than the subsequent loop excision biopsy in small area lesions (lesions ≤ 2 sectors $P = 0.0195$, lesions ≤ 4 sectors $P = 0.0014$). However, the likelihood of undercall by the punch biopsy was not related to lesion size and was noted in 19 (32%) of 59 large area lesions (> 4 sectors) and also in 43 (23%) of 184 small area lesions (≤ 4 sectors).

Discussion

Local destructive treatments for CIN are widely employed in modern gynaecological practice. Although the criteria for assessing suitability for such treatments are well recognized, a small number of women still present with invasive cervical cancer after local destructive treatment (Jordan *et al.* 1985; Ali *et al.* 1986). This could be the result of failure to diagnose occult invasion at colposcopy and by directed biopsy. Our study has shown a poor correlation between the severity of abnormality in colposcopically directed punch biopsies and subsequent diathermy loop excision biopsy specimens.

Overcall in colposcopically directed punch biopsies was related to lesion size and was particularly marked in small area lesions. There are several possible explanations for this observation, including complete removal of the lesion

Table 2. Effect of lesion size on agreement between punch biopsy and loop excision of the transformation zone

No. of sectors involved	Punch biopsy			
	Undercall <i>n</i> (%)	Overcall <i>n</i> (%)	Agreement <i>n</i> (%)	Total <i>n</i> (%)
1-2	21 (23.6)	35 (39.3)	33 (37.1)	89 (100)
3-4	22 (23.2)	29 (30.5)	44 (46.3)	95 (100)
5-6	14 (32.6)	4 (9.3)	25 (58.1)	43 (100)
7-8	5 (31.2)	2 (12.5)	9 (56.3)	16 (100)
Total	62	70	111	243

Difference between undercall, overcall and agreement (χ^2 test): for > 4 sectors $\nu \leq 4$ sectors $\chi^2 = 13.197$, $P = 0.0014$; for > 2 sectors $\nu \leq 2$ sectors $\chi^2 = 7.871$, $P = 0.0195$.

by the directed biopsy, stripping of friable dysplastic epithelium which remains and tissue destruction due to local inflammatory response after the biopsy. An alternative hypothesis is that a directed biopsy has an effect on the biology of intraepithelial neoplasia (Richard & Barron 1969).

Undercall, noted in 32% of large area lesions and in 23% of small area lesions is a particularly worrying feature of this study and is of considerable clinical importance since in 62% of these patients high grade lesions were involved, including three with adenocarcinoma *in situ* and one with early invasive cancer which were missed on punch biopsy. If undercall was largely due to errors by the colposcopist in selecting a biopsy site in large area lesions then a direct association with lesion size would have been expected. However, we found that in over one third of the patients undercall with punched biopsy occurred in lesions occupying no more than two sectors. An alternative explanation is that undercall was the result of disease progression in the interval between punch biopsy and loop diathermy excision, but we consider this to be unlikely in the relatively short time involved.

A factor not considered in this analysis was the potential effect of intra- and inter-observer variability in reporting the grade of lesion. Although this might account for some of the observed discrepancies between paired biopsies, 54% of undercalled CIN 3 lesions in loop specimens showed no abnormality more severe than CIN 1 in the paired punch biopsy. This degree of differ-

ence is unlikely to be the result of variability in reporting the grade of lesions.

The results of our analysis suggest that directed punch biopsy may be an inadequate endpoint for judgement of the severity of an epithelial lesion before local destructive treatment of the cervical transformation zone. Our findings have important implications both for patient management and for trial design and must cast doubt on the results of studies of preinvasive disease using directed punch biopsy as an endpoint.

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Presence of an oestradiol receptor-related protein in the skin: changes during the normal menstrual cycle

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Abstract

Objective—To investigate the presence of an oestradiol receptor-related protein (P29) in skin and skin organelles, and to assess changes in its content during the normal menstrual cycle.

Design—An observational study.

Setting—King's College School of Medicine and Dentistry, London.

Subjects—Twenty-one premenopausal women with regular menstrual cycles undergoing gynaecological surgery. They were allocated to proliferative or secretory phases of the menstrual cycle on the basis of menstrual dating and histological examination of an endometrial sample

Interventions—Small full thickness sections of skin (about 5 mm in depth) taken from the anterior abdominal wall at hysterectomy or laparoscopic sterilization.

Main outcome measures—The concentration of the oestradiol receptor-related protein in skin and its organelles was assessed semi-quantitatively, using a monoclonal antibody technique. The intensity of staining was compared between the proliferative and secretory phases of the cycle.

Results—The receptor-related protein was consistently observed in epidermis, sebaceous glands, hair follicles and sweat ducts; there was no significant difference in its concentration between the proliferative and secretory phases of the menstrual cycle. The protein was not present in dermis and sweat ducts.

Conclusions—Epidermis and some skin organelles contain an oestradiol receptor-related protein and must be considered as oestrogen target tissues. However, the content of this protein does not appear to change significantly during the normal menstrual cycle.

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It is well recognized that androgens have major effects on the skin and its appendages (hair follicles, sweat ducts and sebaceous glands). For example, hyperandrogenic women frequently complain of hirsutism, excessive skin greasiness and acne. However, few gynaecologists appreciate that skin and its appendages are also likely to be oestrogen-dependent.

Clinically, postmenopausal women often complain of thin and dry skin, changes which in our experience appear reversible with oestrogen replacement therapy. Such treatment also increases the skin collagen content (Brinck *et al.* 1983).

Biochemically, oestradiol receptors have been

demonstrated in sections of skin using traditional, ligand-binding methods (Stumpf *et al.* 1974), and their presence suggests that oestrogen effects may be mediated via a traditional sex-steroid receptor mechanism. However, these conventional biochemical techniques rely on tissue homogenates and therefore cannot identify the distribution of the receptor within the various skin organelles. Thus, these methods cannot determine which parts of the skin and its appendages are oestrogen dependent. More recently, immunocytochemical techniques using a monoclonal antibody derived from collaborative work between the Imperial Cancer Research Fund and Amersham International have demonstrated the presence of a protein related to the oestradiol receptor in oestrogen target tissues such as the breast and endometrium.

Measurement of the concentration of this protein has been used as a marker of oestrogen sensitivity, and the technique offers several advantages over that which utilises a monoclonal antibody raised against the oestradiol receptor itself. First, the new technique is suitable for use with paraffin wax-embedded tissue blocks. Second, the oestradiol receptor-related protein is more abundant than the oestradiol receptor itself; in oestradiol receptor positive tissues the receptor-related protein is present in a concentration of at least 1000-fold excess over the oestradiol receptor itself. Quantitatively, the newer technique correlates well with conventional ligand-binding methods (King *et al.*, 1985) and, most importantly, permits identification of individual cells containing the oestradiol receptor-related protein.

In a range of tissues studied thus far, the content of the receptor-related protein is intimately related to the presence or absence of the oestradiol receptor as measured by conventional ligand-binding techniques. With rare exceptions, tissue found to be oestradiol receptor negative by ligand-binding methods does not stain for the receptor-related protein. Although the receptor-related protein content is as good a marker of oestrogen sensitivity as the concentration of the oestradiol receptor itself, there are minor limitations to the technique. For example, it is not suitable for use on frozen sections and, under normal circumstances, it cannot be used on formalin-fixed tissues.

In previous studies, we have shown that the concentration of the receptor-related protein

within endometrial epithelium is significantly reduced by progesterone during the secretory phase of the normal menstrual cycle (Padwick *et al.*, in preparation), and also by progestogens when added to exogenous oestrogen therapy in postmenopausal women (Padwick *et al.* in preparation).

Using similar techniques, the oestradiol receptor-related protein has been demonstrated in normal human skin and its appendages (Jemec & Wojnarowska 1987). In this study we have determined whether the oestradiol-receptor related protein content of skin and its appendages changes during the normal menstrual cycle.

Subjects and Methods

Skin samples were obtained from premenopausal women with a regular menstrual cycle (24–35 days). All women gave informed consent, none was using hormonal contraception or had a history of skin problems. All were non-smokers. Small, full thickness sections of skin (approximately 5 mm in depth) were taken from the anterior abdominal wall at the margin of the incision either at the time of hysterectomy for non-malignant conditions or at laparoscopic sterilization. The samples were fixed in absolute alcohol for 1–2 h and stored in 70% alcohol until analysed. The tissues were wax-embedded and 6 µm thick sections were cut by conventional methods.

The tissue sections were then exposed to the monoclonal antibody (known as 'D5') developed against a protein related to the oestradiol receptor (King *et al.* 1985). This protein has a molecular weight of 29 000 and is called P29. Control samples in which buffer solution was substituted for the specific antibody were always prepared in parallel. All sections were then exposed to a second antibody to D5 which was peroxidase labelled. The presence of the peroxidase is recognized by its ability to convert a diaminobenzidine substrate to an insoluble brown pigment. Thus, cells containing P29 are stained brown by the method and to assist in their identification the sections were lightly counterstained with haematoxylin. The methods have been described in detail (King *et al.* 1985).

The staining intensity of the following skin components was assessed: epidermis, dermis, hair follicles, sebaceous glands, sweat glands and ducts. This was graded without prior knowl-

edge of the phase of the menstrual cycle from 0 (no staining) to 6 (high intensity of stain). All samples were graded by one investigator (D.F.).

Endometrial samples were obtained at the same operation and were examined histologically after conventional staining with haematoxylin and eosin. The features assessed were those of the normal menstrual cycle and the endometrial samples were classified as showing early, mid or late features of either the proliferative or secretory phase. The skin sample was rejected if the endometrial sample showed co-existing proliferative and secretory features, and also if the dating by endometrial examination varied by more than 3 days from the menstrual calendar. If the menstrual history and endometrial histology were in agreement then the skin specimen was classified as either 'proliferative' or 'secretory'.

Statistical methods

Comparisons of age, timing of sample collection and staining intensity for skin and each of the organelles between the proliferative and secretory phase groups was by Fisher's exact test. To compare age, a 2×2 table was constructed comprising the numbers of patients in the two groups above and below the median age of all 21 women. Fisher's exact test was then applied. The same method was used to compare the timing of sample collection except the day of the menstrual cycle (counting the first day of normal bleeding as day 1) was used instead of age. The staining intensity in each of the various skin components were compared the same way except that the 2×2 tables were constructed by summing the numbers of samples scoring 0–3 and those scoring 4–6 for each of the two groups. All of these tables provide data on frequency distri-

bution which whilst essential for analysis is, we believe, of limited value in assisting interpretation of our findings. Therefore, we have presented our results as medians (ranges).

Frequency distribution tables (not shown) were also prepared to compare the staining intensity between the different skin components within the proliferative and secretory phase groups, respectively, and the χ^2 test using the Brandt and Snedecor formula was applied.

Results

Twenty-one skin samples were analysed, 11 in the proliferative group and 10 in the secretory group. Seventeen samples were obtained at abdominal hysterectomy and four (two in each group) at laparoscopic sterilization.

The median age in the proliferative group was 42 years (range 33–53 years) and 44.5 years (range 34–52 years) in the secretory group; there was no significant difference between the two groups. There was a significant difference (Fisher's exact test: $P < 0.01$) in the timing of sample collection between the two groups. The median day of the menstrual cycle when the skin samples were obtained was day 9 (range 3–12) in the proliferative group and day 19 (range 16–30) in the secretory group.

Staining was not observed in any of the control sections.

In the sections exposed to D5, staining was never observed in either the dermis or sweat glands, irrespective of the menstrual phase. Staining was observed in the epidermis (Fig. 1), hair follicles (Fig. 2), sweat ducts (Fig. 3), and sebaceous glands (Fig. 4), and was always contained entirely within the cytoplasm. The staining intensity scores for the epidermis and the three organelles during the proliferative and secretory phases are shown in Table 1.



Fig. 1. Staining of epidermis. Magnification $\times 40$.

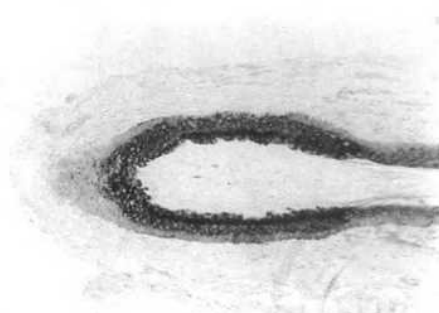


Fig. 2. Staining of hair follicle. Magnification $\times 40$.



Fig. 3. Staining of sweat duct. Magnification $\times 40$.

With the exception of the stratum corneum, the epidermis showed good staining in every sample from both the proliferative and secretory phases, and the intensity appeared uniform within the various epidermal layers (Fig. 1). The intensity of the staining was less in the three organelles, irrespective of the phase of the menstrual cycle. The order of decreasing intensity was hair follicles, sweat ducts and sebaceous glands (Table 1). Not every skin section contained examples of all three organelles. Hair follicles, sweat ducts and sebaceous glands were identified in 8, 10 and 8 of the 11 proliferative-phase samples, and 8, 9 and 8 of the 10 secretory-phase specimens, respectively. Conversely, many sections contained more than one example of one or more organelle, and when this occurred each was scored individually and a mean score was calculated. Every organelle in every sample showed staining but the intensity varied between different samples in the two menstrual phases as is shown by the ranges in Table 1. It has not been possible to illustrate this

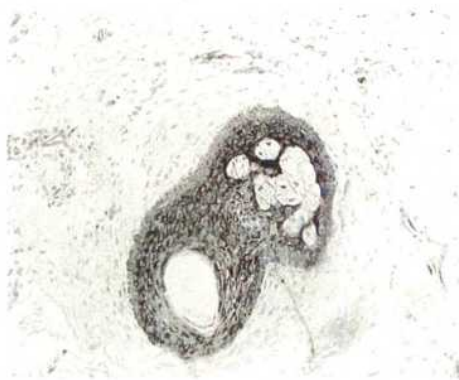


Fig. 4. Staining of sebaceous gland: an adjacent hair follicle is shown in cross-section. Magnification $\times 40$.

variation in staining intensity in one photomicrograph because the organelles were relatively sparse within each specimen. To include three or four examples of the same organelle within one illustration requires such low magnification that details of the individual organelles are not clearly visible.

There were no significant differences between the two groups for the staining intensity of the epidermis and the three organelles (Fisher's exact test).

Comparisons of the staining between the individual organelles within the two phases showed that the epidermis and hair follicles consistently stained more strongly than the sweat ducts and sebaceous glands. This was true for both the proliferative and secretory groups (χ^2 test, $P < 0.05$).

Discussion

Using a monoclonal antibody technique a protein (P29) related to the oestradiol receptor has been identified in skin samples obtained from apparently normal premenopausal women. We have assessed the staining intensity of skin and its appendages from the lower anterior abdominal wall during the proliferative and secretory phases of the normal menstrual cycle.

No staining was observed within the dermis or the sweat glands. The dermis is largely composed of collagen which is produced by fibroblasts. Our negative result confirms the earlier report of Jemec & Wojnarowska (1987), but is at variance with other observations. Using autoradiographic techniques in mouse skin, Stumpf *et al.* (1974) demonstrated incorporation of tritiated oestradiol into the nuclei of some, though not all, fibroblasts. Furthermore, skin collagen content appears to be increased by oestrogen therapy (Brincat *et al.* 1983), although it is unclear whether this effect is mediated through

Table 1. Staining intensity scores for skin and appendages in samples obtained in the proliferative or secretory phase of the menstrual cycle*

	Proliferative (n = 11)	Secretory (n = 10)
Epidermis	4.0 (3–6)	4.0 (3–6)
Sebaceous gland	2.0 (0–4)	2.0 (1–6)
Hair follicle	4.0 (1–6)	4.0 (1–6)
Sweat duct	2.5 (1–4)	2.0 (1–4)

*Staining intensity was graded from 0 to 6 and data are median (range) values.

fibroblast stimulation. Further research is required to explain these conflicting observations.

All staining that we observed was contained within the cytoplasm and was not nuclear. This pattern is identical to that observed in human myometrial and endometrial preparations (Coffey *et al.* 1985a), and provides further evidence that P29 is cytoplasmic. The epidermis stained most intensely (Fig. 1), and this staining appeared uniform within the various epidermal layers the stratum corneum did not stain. Hair follicles also stained moderately intensely (Fig. 2) and this implies moderate concentrations of oestradiol receptor and oestrogen dependence. Thus, it is not surprising that many postmenopausal women report changes in hair quality which are often described, in our clinical experience, as 'lifeless', 'lacklustre' and 'dry'. We are unaware of any longitudinal studies of hair health in women undergoing loss of ovarian function, or of placebo-controlled studies of changes in hair characteristics in postmenopausal women given exogenous oestrogens. Until such studies are performed, the precise relation between oestrogens and hair health will remain controversial but our data provide a mechanism for a beneficial effect.

The same comments apply to sweat ducts (Fig. 3) and sebaceous glands (Fig. 4), although the staining intensity in these organelles was less than that seen with epidermis and hair follicles (χ^2 : $P < 0.05$) in both the proliferative and secretory phases. The reduced intensity in the sweat ducts may be related to a variation in oestradiol receptor content throughout the length of the duct, or to its anatomical arrangement. The sweat gland, which did not stain, lies deep within the dermis. The duct, which constitutes the secretory part of the gland, did stain. This is straight as it traverses the dermis and becomes coiled as it passes through the epidermis. We observed a variation in the staining of the sweat ducts which may reflect differences in staining intensity at different sites along the duct. Alternatively, the staining intensity may be uniform within an individual duct and the differences that we observed were due to the juxtaposition of ducts from different glands within our cross-sectional tissue slices.

We have considered methodological variations as an explanation for the differences in the staining intensity of the epidermis and the organelles that were observed between skin speci-

mens. However, we consider this an unlikely explanation. All skin samples were processed throughout this study in an identical fashion, and the concentration of D5 (30 μ l per slide specimen) and the second peroxidase-labelled antibody (20 μ l per slide specimen) should have been more than sufficient to bind any P29 and D5, respectively.

We failed to demonstrate a change in staining intensity in the epidermis and the three organelles between the phases of the menstrual cycle (Table 1). This is, perhaps, not very surprising because most women do not undergo major alterations in skin and hair health premenstrually. However, it is in marked contrast to changes observed in other oestrogen-dependent tissues. In endometrial glandular tissue, the staining intensity observed in the late proliferative phase is reduced more than 10-fold within 6 days of ovulation (Padwick *et al.*, in preparation). A similar suppression in the endometrial content of the receptor-related protein has been observed within 72 h of progesterone addition to post-menopausal women receiving oestrogen therapy (Padwick *et al.*, in preparation). Thus, the reduction in staining intensity in endometrium appears progestin-mediated.

We did not measure plasma oestradiol or progesterone levels when the skin samples were obtained but relied upon an end-organ response, endometrial transformation. Only skin samples from women showing wholly proliferative or secretory endometrial features were analysed, and the histological picture had to correlate (to within 3 days) with the menstrual history. Thus, we have no doubt that our samples were taken either during the proliferative or secretory phases. Although the majority of skin samples were in the late proliferative or early secretory phases, our previous observations on endometrium leave us in no doubt that there was sufficient time for changes in the receptor-related protein content to occur if skin and its organelles behaves like endometrium. Clearly, it does not. One caveat must be added. Almost all of the hair follicles which we assessed were in telogen and we do not know whether growing anagen hair follicles behave similarly with respect to the lack of change in the content of P29 during the menstrual cycle. Likewise, we caution against extrapolating these results, obtained on skin samples from the anterior abdominal wall, to scalp hair.

Various explanations are available to explain why regulation of P29 in skin and its appendages may be different to that observed within the endometrium. The D5 antibody does not bind to the oestradiol receptor itself, but to a cytoplasmic protein associated to the receptor; nonetheless, on current evidence, only cells that are oestrogen receptor positive (as measured by conventional, ligand-bonding techniques) will stain with the D5 antibody (Coffer *et al.* 1985b). Our current findings may reflect a dissociation of the receptor from the P29 protein, whereby the former is regulated by the conventional sex-steroid receptor binding mechanism whereas the latter is not. This hypothesis might be tested with a monoclonal antibody specific for the nuclear oestradiol receptor. Such methods are available (King & Greene, 1984) but have not been applied to changes in skin during the menstrual cycle.

An alternative explanation is that the protein content may be regulated—but because the concentration of P29 is so much greater than that of the oestradiol receptor, subtle changes in the amount of P29 which are induced by fluctuations in plasma oestradiol or progesterone may not be detected by the technique that we used.

Although the role of P29, the means whereby its content is regulated, and the manner in which it regulates gene expression are unknown or poorly understood, it is clear that the epidermis, hair follicles, sweat glands, and sebaceous glands stain for it and thereby, on current thinking, appear to be oestrogen dependent.

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Assessment of urinary symptoms in early pregnancy

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Abstract

Objectives—To determine the correlation between lower urinary tract symptoms and urodynamic findings in early pregnancy.

Setting—The termination clinic and gynaecology ward at King's College Hospital.

Design—Observational study.

Subjects—47 women before termination of pregnancy at between 6 and 15 weeks.

Interventions—Women filled in symptom questionnaires and then had urodynamic investigations, consisting of uroflowmetry and subtracted provoked cystometry.

Main outcome measures—The occurrence of lower urinary tract symptoms and their association with urodynamic findings.

Results—Lower urinary tract symptoms were fairly common but there was poor correlation with the urodynamic findings.

Conclusions—The findings suggest that lower urinary tract symptomatology alone is insufficient to study lower urinary tract dysfunction in pregnancy.

Urinary symptoms are known to be very common in pregnancy but their correlation with lower urinary tract dysfunction has not been determined. There have been three major reports looking at the occurrence of urinary symptoms in pregnancy. Francis (1960a) and Stanton *et al.* (1980) assessed urinary frequency throughout pregnancy. In addition, Francis (1960b) determined the rate of stress incontinence and Stanton *et al.* (1980) assessed that of both stress incontinence and urge incontinence. There are few data relating to the occurrence of urgency alone or the symptoms of voiding difficulties.

Little has been published describing results of urodynamic investigations in early pregnancy

and even less relating these to urinary symptoms. Francis (1960a) examined the correlation between bladder capacity and frequency of micturition. Iosif *et al.* (1981) compared urodynamic findings in women with and without stress incontinence but they used single channel cystometry only.

To understand the underlying pathophysiology, urinary symptoms in pregnancy must be related to bladder function. We assessed the relation between urinary symptoms and urodynamic findings in women during early pregnancy.

Subjects and methods

Forty-seven women about to undergo termination of pregnancy to protect their mental health were included in the study. All women gave written informed consent and the study had full local ethics committee approval. Those with an acute lower urinary tract infection, previous treatment for urinary symptoms or marked urinary symptoms predating that pregnancy were excluded.

All women completed both a symptom ques-

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tionnaire with reference to their voiding habits and a visual analogue score for symptoms of stress incontinence, urgency, urge incontinence, poor stream and sensation of incomplete bladder emptying. All questions were completed under the guidance of one doctor to prevent question bias. The visual analogue score was graded from 1 to 8, the scoring was 1 for no symptoms, 2 to 3 for mild symptoms, 4 to 5 for moderate symptoms and 6 to 8 for severe symptoms.

A urodynamic assessment was made immediately before the termination. This included uroflowmetry with determination of the peak flow rate and volume voided. A filling catheter and a 1 mm fluid filled pressure catheter were then passed into the bladder and a 2 mm fluid filled tube attached to a pressure balloon was passed into the rectum. The urinary residual was determined. Subtracted provoked cystometry was performed. The bladder was filled with 0.9% saline at room temperature with the woman in the supine position and the first sensation to void and bladder capacity were determined. While erect the woman was asked to cough and then to heel-bounce and any rise in detrusor pressure or leakage determined. Detrusor pressure and peak flow rate were measured during voiding while the woman was seated. Provocative tests used were fast-filling, coughing, change in position from supine to erect and heel bouncing. After termination of pregnancy, the women were returned home with prophylactic antibiotics.

The Mann-Whitney *U* test and Fisher's exact test for the comparison of two proportions were used to analyze the data. Definitions and units conform to the standards proposed by the International Continence Society (Abrams *et al.* 1990).

Results

Of the 47 women in the study, 26 were nul-

liparous and 21 were parous; 28 women were black, 18 were Caucasian and one was Indian. Their ages ranged from 18 to 41 years (median 23). Gestational age ranged from 6 to 15 weeks (median 11 weeks).

Nineteen women (40%) complained of frequency (≥ 7 daytime voids) and 11 (23%) of nocturia (≥ 2 nocturnal voids). Other lower urinary tract symptoms are detailed in Table 1.

On subtracted cystometry 11 women (23%) had phasic detrusor contractions, one had only systolic contractions, seven only provoked and three both systolic and provoked contractions. These contractions resulted in leakage in four women. Genuine stress incontinence was diagnosed in two women. Only one woman had a significant residual urine volume of 80 ml. Other urodynamic findings are presented in Table 2.

We found no significant difference in either the first sensation to void or the bladder capacity between women with and without frequency or nocturia.

Table 3 compares the occurrence of phasic detrusor instability in women with and without urinary symptoms. Detrusor instability appeared to be more common in women who complained of symptoms of urgency and urge incontinence but these differences were not significant. Of the four women who leaked with an unstable detrusor contraction, three complained of urgency and two of these also had urge incontinence. Only one of the two women with genuine stress incontinence complained of the symptom of stress incontinence.

Three women had a peak flow rate <15 ml/s, for a volume voided of >150 ml, but only one of them complained of a poor stream. Urethral resistance was calculated as the maximum voiding pressure divided by the peak flow rate squared. Comparing those women with and without the symptom of a poor stream, there was no significant difference in either peak flow rate, voiding pressure or urethral resistance ($P=0.37$, $P>0.5$, $P>0.5$).

Table 1. Lower urinary tract symptoms in early pregnancy in 47 women

Symptom	Grade of symptom			
	Absent	Mild	Moderate	Severe
Urgency	18 (38%)	13 (28%)	7 (15%)	9 (19%)
Urge incontinence	38 (81%)	3 (6%)	3 (6%)	3 (6%)
Stress incontinence	40 (85%)	5 (11%)	2 (4%)	0 (0%)
Poor stream	33 (70%)	8 (17%)	5 (11%)	1 (2%)
Incomplete emptying	32 (68%)	8 (17%)	5 (11%)	2 (4%)

Table 2. Urodynamic findings in 47 women in early pregnancy

	No. of women	Median range
Peak flow rate (PFR)* (ml/s)	31	25 (10–55)
First sensation (ml)	47	150 (30–300)
Bladder capacity (ml)	47	400 (150–500)
Voiding pressure (VP) (cm H ₂ O)	42	42 (15–75)
Urethral resistance (VP/PFR ²) (cm H ₂ O s ² /ml ²)	42	0.19 (0.03–0.94)

*Only women who voided at least 150 ml had their peak flow rate determined

Discussion

Francis (1960a) noted that 60% of women in early pregnancy had urinary frequency and Stanton *et al.* (1980) found that 45% had urinary frequency and 22% nocturia. Francis (1960b) found that in the first trimester of pregnancy 16% of women complain of stress incontinence and Stanton *et al.* (1980) reported stress incontinence in 16% and urge incontinence in 4%.

Our results on frequency and nocturia agree with those reported by Stanton *et al.* (1980). These rates are slightly lower than those reported by Francis (1960b), probably due to the use of different definitions.

The occurrence of stress incontinence in our subjects was similar to that reported by Francis (1960b) and Stanton *et al.* (1980), but only half that found by Francis. However, we found a comparatively high rate of urge incontinence (18%). We were unable to find any data in previous papers with which to compare our findings in relation to urgency or symptoms of voiding difficulty.

Francis (1960b) found an average bladder capacity in the first trimester of 410 ml, which is similar to our value of 400 ml. In agreement with her paper we found no correlation between bladder capacity and frequency of micturition. In addition we found no correlation between bladder capacity and nocturia.

Those symptoms pertaining to possible detrusor instability were especially common, with 62% complaining of urgency and 18% of urge incontinence. Although our observations are such that these symptoms might occur more often in women with urodynamically proven

detrusor instability, the differences were not significant. It is possible that some detrusor instability failed to be demonstrated by urodynamic testing. Indeed Benness *et al.* (1989) have shown that by repeating urodynamic investigation in symptomatic women, there is an increased detection of detrusor instability. However, it is unlikely that this would explain the very poor correlation we found between the symptoms of an unstable bladder and the diagnosis of detrusor instability.

Iosif *et al.* (1981) compared urodynamic findings in pregnant women with and without stress incontinence. They found, on urethral pressure profilometry, that there was a significant difference in maximum urethral pressure and functional urethral length between the two groups. However Versi (1990) has shown that urethral pressure profilometry is a poor test for diagnosing genuine stress incontinence. The symptom of stress incontinence was present in 15% of our subjects but a diagnosis of genuine stress incontinence was only made in two women and in all only six leaked during urodynamic testing.

Overall 30% complained of a poor stream and 32% of incomplete bladder emptying, but this was not confirmed by urodynamic findings and there was no difference between those with and without these symptoms. It is possible that increased frequency resulted in smaller volumes of urine being passed with each void and thus a sensation of a poor stream.

In summary, urinary symptoms are very common in early pregnancy but in most women they are not associated with abnormal urodynamic results. Some previous studies on lower urinary tract function in pregnancy have assumed diagnoses from the presence of symptoms. We have shown that this is unreliable and that urodynamic assessment is necessary if the true

Table 3. Prevalence of detrusor instability (DI) in women with and without urinary symptoms

Symptom	n	DI	P*
Urgency	29	8 (28%)	0.73
No urgency	18	3 (17%)	
Urge incontinence	9	3 (33%)	0.68
No urge incontinence	38	8 (21%)	
Stress incontinence	7	—	0.33
No stress incontinence	40	11 (28%)	

*Significance of difference in prevalence of detrusor instability between women with and those without urinary symptoms, Fisher's two tailed test.

occurrence of lower urinary tract dysfunction in pregnancy is to be determined.

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Sensory urgency: how full is your bladder?

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Abstract

Objective—To investigate whether women with sensory urgency have an abnormal perception of bladder fullness.

Design—Prospective observational study.

Setting—Urodynamic Unit, St George's Hospital, London.

Subjects—15 women with sensory urgency, 15 women with idiopathic detrusor instability and 15 without symptoms of frequency or urgency (control group).

Interventions—All the women attended for cystometry. Each was asked to complete a visual analogue score of how full she perceived her bladder to be on a scale from 1 to 10. This was done before filling cystometry and at three times during bladder filling. At each time actual filled volume was noted.

Main outcome measures—Maximum bladder capacity and individual perception of bladder fullness.

Results—Women with sensory urgency and detrusor instability had similar maximum bladder capacity although values in both groups were significantly lower than in the control group; thus percentage of maximum bladder capacity was used for analysis. Linear regression was performed for each group of patients and a predicted visual analogue score at 25, 50 and 75% of capacity calculated. These were compared between groups by rank analysis of variance. There was no significant difference between sensory urgency and detrusor instability. However, at 25, 50 and 75% of capacity, both groups had a significantly higher score than the control group.

Conclusions—This abnormal perception would explain symptoms of frequency and urgency in these two groups. These results also confirm the similarity between detrusor instability and sensory urgency.

Sensory urge incontinence has been defined as involuntary loss of urine associated with a strong desire to void which is not due to uninhibited

detrusor contractions and has been called a hypersensitivity dysfunction (International Continence Society 1990). Patients with sensory urgency have a history usually indistinguishable from those with detrusor instability but without the associated pressure rises on filling cystometry. The prevalence of sensory urgency in women attending urodynamic clinics has been estimated at 6% as compared with 31% for detrusor instability (Peattie *et al.*, 1988).

Sensory urgency is usually treated with the same drugs as detrusor instability. Its aetiology, like that of detrusor instability, is unknown and drug treatment is often unsuccessful. Behavioural methods such as bladder drill (Jarvis & Miller

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1980), biofeedback (Cardozo *et al.* 1978; Peattie *et al.* 1988), psychotherapy (Macaulay 1988) and hypnosis (Freeman & Baxby 1982) have all been used. Success rates of over 80% were achieved in all these reports and this might imply an underlying psychological cause.

Patients with anorexia nervosa have been shown to have a distorted body image. When asked to indicate their own perception of their body size, they have been shown to consistently over estimate (Slade *et al.* 1973). This study was designed to determine whether patients with sensory urgency have an analogous abnormal perception of bladder fullness.

Subjects and methods

All definitions and terms used are in accordance with the terminology developed by the International Continence Society (1990). All the women who attended the urodynamic unit for cystometry were asked to participate in the study. They were requested to attend with a comfortably full bladder and on arrival at the unit indicated their perception of bladder fullness on a visual analogue scale from 0 to 10, with 0 as empty and 10 as full. They voided and the amount of urine passed (together with any residual urine) was recorded. Subtracted twin channel cystometry was performed with a filling rate of 100 ml/min. Provocative measures such as cough and hand washing were used. The visual analogue scale was repeated at the first desire to void, at a random time during filling and at maximum desire to void. At each time the actual bladder volume was recorded as a percentage of maximum capacity.

Following interpretation of cystometry, three groups were chosen for analysis. These were consecutive patients falling into one of three clearly defined diagnostic categories; 15 with a diagnosis of sensory urgency based on clinical history of frequency, urgency and urge incontinence and stable cystometry, 15 with frequency, urgency and urge incontinence and detrusor instability on cystometry and 15 with no complaints of frequency, urgency or urge incontinence and stable cystometry. This last group included women who were attending the unit with complaints of only stress incontinence. Symptoms of frequency and urgency were excluded in this group by a careful history and a urinary diary. They form the comparison group.

All patients had a negative urine culture and frequency was determined with a urinary diary.

The visual analogue scores for each patient were regressed against the percentage of maximum bladder capacity. The regression lines were used to predict the visual analogue score for each individual at 25, 50 and 75% of maximum bladder capacity. These scores were then compared between groups by two way rank analysis of variance. It is not possible to simply record maximum bladder capacity and then repeat the cystometry asking each patient to record a visual analogue score at 25, 50 and 75% of maximum bladder volume, as the maximum cystometric capacity is believed to improve with repeated bladder filling.

Results

A total of 45 women were studied and their ages and parity are shown in Table 1. Although the patients were not matched, their clinical features are similar.

The mean maximum bladder capacity of patients with sensory urgency and detrusor instability was similar at 376 ml (SD 129 ml) compared with 376 ml (SD 140 ml) ($P = 0.98$). The comparison group had significantly larger mean maximum bladder capacity than either of these groups at 475 ml (SD 83 ml) ($P < 0.01$) and so percentage of maximum bladder capacity was used for regression analysis.

Linear regression adequately described the data for each woman; quadratic terms being insignificant at the 5% level. There was no statistically significant difference in the mean visual analogue score at 25, 50 and 75% of maximum bladder capacity between the women with sensory urgency and those with detrusor instability (Fig. 1). Figure 1 demonstrates the predicted visual analogue score from all patients. There was no significant difference between those patients with sensory urgency and those with detrusor instability. However, at 25, 50 and 75%

Table 1. Age and parity in the three groups of women investigated

	Sensory urgency (<i>n</i> = 15)	Detrusor instability (<i>n</i> = 15)	Comparison group (<i>n</i> = 15)
Age (years)	48.4 (21–72)	51 (34–85)	46.2 (19–66)
Parity	2.1 (0–4)	2.1 (0–4)	2.3 (0–7)

Results are mean (range) values.

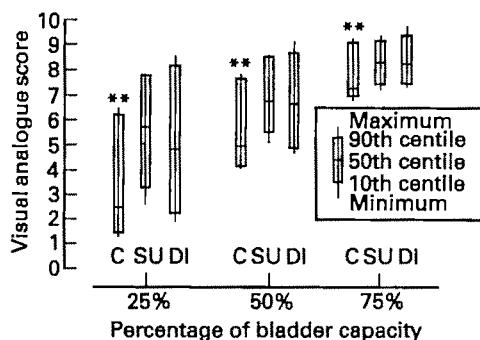


Fig. 1. Box and whisker plots of the predicted visual analogue scores at 25, 50 and 75% of maximum cystometric capacity for women without complaints of urgency or frequency (C), those with sensory urgency (SU) and those with detrusor instability (DI). Rank analysis of variance shows that women in group C had significantly lower perception of bladder fullness (** $P < 0.01$) at each point; no differences were observed between women in the other two groups

of maximum bladder capacity, both these groups had a significantly higher visual analogue score than the comparison group.

Discussion

The aetiology of sensory urgency is unknown but a psychological component is likely. Women with detrusor instability and sensory urgency have been shown to be significantly more anxious and neurotic when tested by the Eysenk personality questionnaire (Crisp & Sutherst 1983, Pierson *et al.* 1985; Macauley *et al.* 1985). The role of a psychological component is also suggested by the success of behavioural techniques such as bladder drill (Jarvis & Millar 1980), biofeedback (Cardozo *et al.* 1978; Peattie *et al.* 1988), psychotherapy (Macauley 1988) and hypnosis (Freeman & Baxby 1982).

Our results show that women with sensory urgency are indistinguishable from those with detrusor instability in their perception of bladder fullness. This lends support to the theory that they may share similar aetiology and may indeed be variations of the same condition (Freeman 1984).

Our results clearly demonstrate that women with sensory urgency and detrusor instability have abnormal perceptions of bladder fullness at 25, 50 and 75% of maximum bladder capacity compared with women who have no complaints of frequency or urgency. The desire to pass urine

depends on perception of bladder fullness and with increasing fullness the desire becomes more urgent, hence this abnormal perception of bladder fullness explains the symptoms of frequency and urgency experienced by patients with sensory urgency and detrusor instability. The reason for this may be a local change in the bladder or an alteration in the subconscious cerebral control of bladder filling but the cause of this overestimation remains to be determined.

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Pregnancy in Crigler-Najjar syndrome. Case report

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Case report

A 21-year-old woman known to have Crigler-Najjar syndrome presented at 14 weeks gestation in her fifth pregnancy. Her first three pregnancies were terminated by first trimester therapeutic abortion on social grounds, and her fourth pregnancy ended in miscarriage. Liver function tests performed before termination of pregnancy in 1986 showed a bilirubin concentration of 460 $\mu\text{mol/l}$.

This pregnancy was planned and her general health was good, but she had hepatomegaly and mildly deranged liver function tests. At her booking visit she was profoundly jaundiced, without evidence of hepatic encephalopathy. All other investigations were normal.

At 21 weeks gestation she complained of right hypochondrial pain, and pruritus became noticeable beyond 25 weeks with slight tremor of the hands. There was no relation to the bilirubin level. Mental alertness remained unaltered. Bilirubin level remained consistently elevated during her pregnancy (Table 1).

Serial ultrasound examinations at 25, 30 and 36 weeks gestation showed a normal growth pattern.

Labour was induced at 41 weeks by forewater amniotomy via an amnioscope and oxytocin infusion. The amniotic fluid was yellow, thick and gelatinous. Its optical density (OD 450 nm)

was estimated to be 0.36. (Normal upper limit at term 0.02).

The fetal cardiotocograph remained normal throughout. Epidural analgesia was established after 6.5 h. After 13 h of uncomplicated labour she had an unexplained grand mal seizure; spontaneous recovery occurred after several minutes. Neurological examination was normal with no evidence of hepatic encephalopathy, and she remained normotensive. There was no proteinuria, her electrolytes were normal and blood glucose was 9 mmol/l. She was delivered by caesarean section of a male infant with Apgar scores of 8 and 10, at 1 and 5 min respectively. On the fifth postpartum day she discharged herself. On review at the gastroenterology clinic she appeared very well, and had no further fits, but did not attend for EEG and C/T scan of head.

At birth the baby was markedly icteric with an umbilical cord bilirubin of 410 $\mu\text{mol/l}$ (conjugated 193). The haemoglobin was 14.4 g/dl, and birthweight was 4.13 kg. Phototherapy was instituted for 24 h, with good response. Initial neurological assessment was satisfactory, but at 9 months there was delay in reaching for objects. He tended to 'fist' and limb tone was raised in all 4 limbs—left more than right. A CT brain scan showed no abnormality. At 18 months there was an evolving quadriplegia but cognitive development seemed satisfactory.

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Discussion

Severe unconjugated hyperbilirubinaemia is extremely rare in adult life, and pregnancy even more so. It was therefore difficult to predict the effect of this degree of maternal jaundice on the fetus. This syndrome was first described by Crigler & Najjar (1952) and most affected individuals die in the first year of life with kernicterus. The conjugating enzyme UDP glucuronyl transferase (UDPGT) is undetectable in liver, and

Table 1. Maternal liver function tests throughout pregnancy in a woman with Crigler-Najjar syndrome

Gestation (weeks)	Total bilirubin ($\mu\text{mol/l}$)	Alanine transferase (IU)	Alkaline phosphatase (IU)
14	363	91	71
17	387	90	86
19	366	57	101
21	360	88	118
23	358	118	116
25	378	109	135
27	371	135	144
29	458	205	125
31	402	184	177
33	366	111	158
38	390	67	256
39	405	137	278
40	357	136	265
41	420	76	342

serum bilirubin concentrations are usually in excess of 250 $\mu\text{mol/l}$. A milder familial form has been described (Arias 1962) in which there is partial absence of UDPGT and bilirubin is rarely more than 150 $\mu\text{mol/l}$.

A successful outcome of pregnancy has recently been described in Eire in this milder form of Crigler-Najjar syndrome type 2 (Cahill & McCarthy 1989). The authors record a highest maternal bilirubin of 107 $\mu\text{mol/l}$. It is not possible to be certain of the type in our patient, but the level of bilirubin is more in keeping with the complete absence of UDPGT (type 1).

In pregnancy the mechanism of bilirubin conjugation changes as the fetus develops and the conjugating capacity is greater than in the adult (Tanner 1989). Unconjugated bilirubin is transported across the placenta from fetus to mother by active transport but there is conflicting evidence of transport in the opposite direction. In this case exposure to high levels of unconjugated bilirubin *in utero* may be associated with the now evolving quadriplegia, despite prompt treatment and a good response to phototherapy at birth. The confounding factor is the maternal seizure, although the Apgar score at birth was normal.

Antenatal phototherapy to the mother was

not used as experience in adults is limited (Wolkoff *et al.* 1979). The mother remains well in spite of her severe jaundice but the outlook for further pregnancies must be much less optimistic than previously. Inheritance is dependent upon which type of Crigler-Najjar syndrome affects the mother. Type 1 can be associated with consanguinity (Crigler & Najjar 1952) and is transmitted as an autosomal recessive (Arias *et al.* 1969). Whereas type 2 is less clear, with both autosomal dominant with incomplete penetrance (Arias *et al.* 1969) and autosomal recessive inheritance (Hunter *et al.* 1973) being suggested.

Acknowledgments

We are very grateful to Professor Barbara Billing, Professor R. W. Cooke and Dr R. P. H. Thompson for their advice on the investigation and management of this patient.

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Maternal trauma and cerebral lesions in preterm infants. Case reports

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Case reports

Patient 1

A healthy primigravida had an uneventful early pregnancy with normal booking scan at 18 weeks. At 29 weeks, a car travelling at approximately 25 mph struck her on the right side resulting in fractures of her right humerus and fibula. She complained of right sided abdominal pain but there was no accompanying vaginal bleeding. A cardiotocograph (CTG) showed decelerations and uterine activity. She was transferred to the regional unit where CTG, uteroplacental Doppler waveforms and ultrasound of the fetus and placental site were normal. She remained under observation and 2 weeks later, having previously been normotensive, she developed pre-eclampsia (blood pressure 170/110, proteinuria 2+). One dose of intravenous hydralazine and maintenance oral methyldopa gave good blood pressure control. Three days later at 31½ weeks she went into preterm labour and had an uncomplicated vaginal delivery of a female infant weighing 1.46 kg with a head circumference of 27.5 cm (both 50th centile) and Apgar scores of 9 and 10 at 1 and 5 min. The placenta was of appropriate weight for gestation with no retroplacental clot. The baby did not require any

ventilatory support and oral feeds were given from 12 h of age. Cranial ultrasound scan at 6 h of age showed bilateral intraventricular haemorrhages (IVH) with casts that already showed signs of resolution with clot retraction (Fig. 1A). Initial haemoglobin concentration was 16.4 g/dl, platelet count $278 \times 10^9/l$ and coagulation screen was normal. Repeated cranial ultrasound scans showed no significant ventricular dilatation and uneventful resolution of the IVH. Neurological examination at 12 months was normal.

Patient 2

A 21-year-old primigravida, 1.5 m in height, who smoked 20 cigarettes a day had an uneventful early pregnancy with normal scan at 16 weeks. At 27 weeks, she fell onto her abdomen while travelling on a bus. An episode of vaginal bleeding after this resolved uneventfully. An ultrasound scan of placenta showed no abnormality and no comment was made of fetal size. At 30 weeks, she was admitted for investigation of decreased fetal movements. CTG showed unprovoked decelerations and ultrasound scan showed a small for gestational age fetus with reduced amniotic fluid volume. A female infant was born by emergency caesarean section. She weighed 750 g, had a head circumference of 24.5 cm (<3rd centile) and Apgar scores of 5 and 7 at 1 and 5 min. The placenta was small (180 g) and healthy, and there was no retroplacental clot. The baby was intubated at birth and ventilated for mild respiratory distress for 4 days. Cranial ultrasound scan at 5 h of age showed bilateral PVH/IVH with a large echodensity extending well into the parenchyma on the left (Fig. 1B), which showed cystic changes

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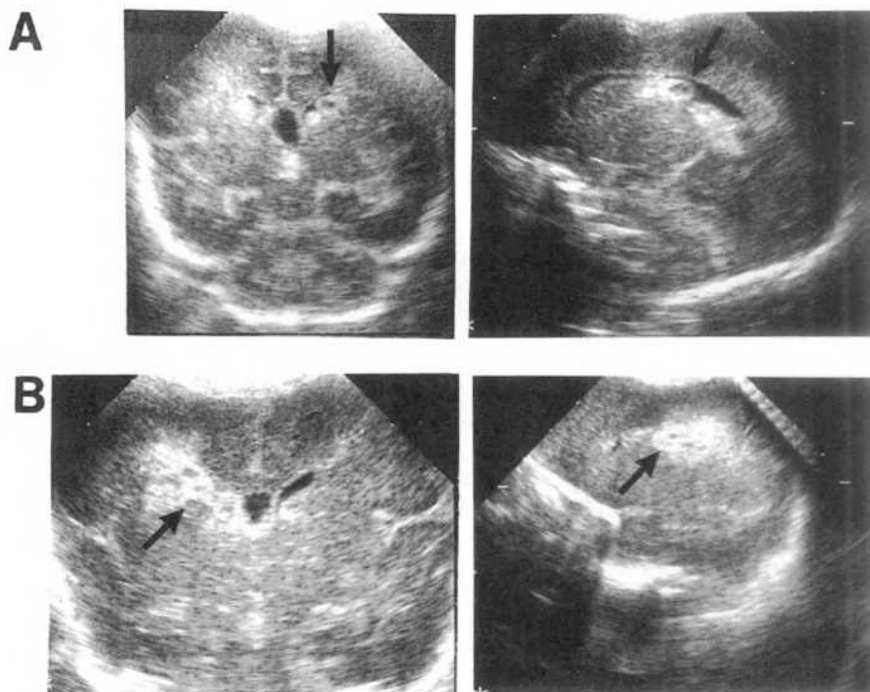


Fig. 1. Coronal and parasagittal cranial ultrasound scans of the two infants. A—Patient 1 at 6 h of age showing bilateral intraventricular haemorrhages, with cystic change on the right (arrow). B—Patient 2 at 21 h of age showing bilateral intraventricular haemorrhage with periventricular cystic changes on the left (arrow).

within 24 h. Her initial haemoglobin was 15.0 g/dl and platelet count $61 \times 10^9/l$. She developed necrotizing enterocolitis on day 23 and died on day 29. Post-mortem showed evidence of old clot in the cisterna magna and cystic periventricular leucomalacia in the left centrum semiovale and both occipital lobes. Chromosome analysis showed her to be a Turner mosaic (XO/X ring X).

Discussion

Several reports have described cerebral lesions in term infants that can be attributed to trauma in pregnancy. (Larroche 1986; Morey *et al.* 1981).

Direct trauma to the mother can lead to fetal injury and descriptions of a battered infant with IVH following repeated abdominal trauma have been reported in an infant born at term (Morey *et al.* 1981). Fetal death and injury are increased by placental abruption as the result of seat belt restraint during road traffic accidents (Chetcuti & Levene 1987; Pepperell *et al.* 1977). Larroche (1986) described three term infants with fetal

cerebral injury after involvement in road traffic accidents without obvious maternal physical injury. It is difficult to know whether the injury could be due to direct fetal trauma or subsequent maternal shock. Myers (1975) demonstrated that psychological stress to a pregnant monkey may cause associated ischaemic injury to her fetus via activation of the maternal sympathetic nervous system. We were unable to find any previous case reports of preterm infants whose cerebral lesions can also be attributed to antenatal maternal trauma. Both of our infants were born some weeks after the accidents and for reasons not related to their accidents. Neither placenta showed evidence of abruption nor retroplacental haemorrhage either on scanning at the time of the accidents, or on examination after delivery. The cerebral lesions noted soon after birth could not be attributed to more recent antenatal or intrapartum insults. It would appear that despite reassuringly normal assessments at the times of the traumatic incidents, transient abnormalities of placental flow could be implicated in the aetiology of these cerebral lesions in preterm infants.

Acknowledgments

We thank Professor M. Elder for permission to report on his patients.

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Retention of the second twin: a viable option?

Case reports

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Case reports

Patient no. 1

A 38-year-old woman presented in her second pregnancy, her first pregnancy was uncomplicated and ended at term. Twins had been diagnosed in this pregnancy and she was referred at 15 weeks gestation to King's College Hospital for an amniocentesis because of maternal age. An ultrasound scan before the amniocentesis confirmed the gestational age and demonstrated an upper and lower sac. A double puncture technique was used to obtain amniotic fluid samples and the fetal karyotypes were normal. Three days after the amniocentesis she presented to her local hospital with spontaneous rupture of the chorio-amniotic membranes of the lower sac. At 19 weeks gestation she was reviewed at King's College Hospital and a follow-up ultrasound scan confirmed oligohydramnios of the lower sac. All measurements of twin I were below the 5th centile but twin II was growing normally with a normal amount of amniotic fluid. After full discussion with the parents a decision was made to allow the pregnancy to continue. At 21 weeks gestation ultrasound examination revealed persistent oligohydramnios in the lower sac with growth of twin I just

below the 5th centile. Twin II was still growing normally with normal amniotic fluid volume. The woman was readmitted at 23 weeks gestation with an episode of vaginal bleeding. Two days after admission she developed a pyrexia with tachycardia and antibiotic treatment was started after appropriate swabs had been taken. The uterus became irritable and two days later she complained of a firm mass at the vulva which was found to be a fetal head. Extraction of the fetus was not possible until a general anaesthetic had been administered. The fetus was then gently extracted with the aid of a bivalve speculum, used in the manner of obstetric forceps to the head. The umbilical cord was cut and trimmed at the cervix. Ultrasound examination confirmed an intact second sac with the fetal heart still beating and a conservative approach to further management was adopted. Treatment with antibiotics was continued and nifedipine and ritodrine were prescribed. Over the next 13 days all remained well. At 25 weeks gestation the woman reported an increasing vaginal discharge and an ultrasound scan suggested a slight reduction in amount of amniotic fluid. The vaginal discharge continued and a subsequent scan performed several days later revealed oligohydramnios. At 26 weeks and 5 days gestation, 11 weeks after initial membrane rupture and 21 days after the first twin had been extracted, labour supervened. Shortly after the onset of labour a live female infant was born spontaneously with the aid of an episiotomy. The placenta was born by cord traction. Postnatal recovery was uncomplicated. On the second day post partum the placenta of twin I, which had been presumed to have been resorbed, was passed spontaneously. Histological examination of the placentas confirmed the dichorionic, diamniotic nature of the pregnancy with 100% infarction of the smaller placenta.

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Neonatal course. The baby weighed 1080 g and had Apgar scores of 5 and 9 at 1 and 5 min respectively. She was electively intubated and intermittent positive pressure (IPPV) was given from birth but she was breathing air by the second day of life and had no further respiratory problems. In view of the prolonged rupture of membranes the baby was given antibiotics for six days after birth but all bacteriological cultures were negative. Oral feeds were started on the third day and she was returned with her mother to the referring hospital one week after the birth. Examination of the infant at 27 weeks of age confirmed that she was healthy and developing normally. Her weight, length and head circumference were all above the 50th centile. She is now 3 years old and well.

Patient no. 2

A 34-year-old woman in her seventh pregnancy had previously given birth to a live girl after induction of labour at 38 weeks gestation for pregnancy-induced hypertension and she subsequently had two first trimester miscarriages, followed by a spontaneous vaginal delivery at 40 weeks gestation and two more first trimester miscarriages. In the current pregnancy she booked at 13 weeks when she gave a history of chronic mild asthma. An ultrasound examination at 15 weeks gestation revealed a twin pregnancy and a further scan at 20 weeks showed that all measurements of both the twins were on the 50th centile. However, a subsequent ultrasound scan at 23 weeks showed no growth in twin I but normal growth in twin II. At this time her asthma worsened due to a chest infection. She was given penicillin and aminophylline and the infection resolved. She presented at 23 weeks and 5 days gestation with vaginal bleeding and she was then admitted to hospital for observation. Three days later twin I was miscarried and the umbilical cord was cut and trimmed at the cervix. Conservative management was continued and the cervix remained closed. Cefuroxime and metronidazole were given for five days. An ultrasound scan at 25 weeks gestation showed that twin II was growing normally but shortly after this rupture of the second sac occurred. An amniocentesis was performed which showed pus cells and scattered cocci and the patient was again given cefuroxime and metronidazole. One day later she became febrile and complained of uterine contractions. Labour

was stimulated with oxytocin, followed by the birth of a live girl. The third stage led to uncomplicated delivery of both placentas.

Postnatally the mother continued with a seven day course of the antibiotics and her recovery was uncomplicated.

Neonatal course. The baby weighed 860 g and had Apgar scores of 2 and 7 at 1 and 5 min respectively. She required IPPV for 18 h, then she was extubated and given supplemental oxygen in a headbox. At 3 weeks of age IPPV had to be given again due to recurrent apnoeic attacks associated with bradycardia. By 1 month of age the baby was breathing air. The only other problem was the need for a skin graft of an intravenous infusion site after development of a localized abscess due to *Escherichia coli*. She was discharged home at 68 days of age and at 25 months she is thought to be neuro-developmentally normal. Her height and weight are within the normal range.

Patient no. 3

A 36-year-old woman in her second pregnancy was found to have twins after in-vitro fertilization (IVF). Her first pregnancy had also followed IVF and ended with the delivery at 29 weeks gestation of a severely growth retarded baby weighing 539 g who subsequently died at 2 weeks of age. In the current pregnancy an ultrasound scan at 16 weeks confirmed the twin pregnancy with the biparietal diameter (BPD), head circumference (HC) and abdominal circumference (AC) for twin I on the 45th, 20th and 5th centiles, respectively, and the same measurements for twin II were on the 40th, 20th and 20th centiles, respectively. An ultrasound scan at 21 weeks showed that growth had been maintained, but another scan at 23 weeks and 5 days demonstrated that the AC had dropped to the 5th centile in twin II and below the 5th centile in twin I. Two further ultrasound scans showed that the growth of twin II was maintained but the growth of twin I had slowed markedly and the intra-uterine death of twin I occurred at 26 weeks and 5 days gestation. Dexamethasone, 24 mg in divided doses, was administered at 27 weeks and an ultrasound scan at 28 weeks and 5 days showed that the growth of twin II had fallen to the 3rd centile. At 29 weeks and 5 days gestation the woman developed abdominal discomfort and shortly afterwards twin I was stillborn and the cord was cut. After discussion with the parents a

decision was taken to continue to manage the pregnancy conservatively. Weekly ultrasound scans demonstrated a continued reduction in the rate of growth of the remaining twin. At 32 weeks gestation a live male infant was born by caesarean section. The mother made an uneventful recovery.

Neonatal course. The birthweight was 1100 g and Apgar scores were 8 and 9 at 1 and 5 min. Supplemental inspired oxygen was initially required but the concentration was rapidly reduced and the baby was soon breathing air. Antibiotics were administered initially but were stopped when negative bacteriological cultures were obtained. A brief hypoglycaemic episode was treated with intravenous dextrose and did not recur. Thrombocytopenia was found on day 2 and persisted for the first week. At 10 days he developed abdominal distension and the radiographic appearance was consistent with non-specific dilatation of the small and large bowel. This resolved after a period of parenteral feeding. *Staphylococcus epidermidis* septicaemia at 15 days was treated with intravenous vancomycin. He developed conjugated hyperbilirubinaemia and abnormal liver function tests from the age of three weeks. After extensive investigation this was thought to be due to neonatal cholestasis associated with prolonged parenteral nutrition and sepsis. The jaundice gradually resolved and the baby was discharged at 57 days old. When last seen at a chronological age of 48 weeks he was noted to be a tall and thin boy whose neuro-developmental progress was normal.

Patient no. 4

A 31-year-old woman booked at 8 weeks gestation in her second pregnancy. Her previous pregnancy had resulted in a 4.2 kg baby girl born by Neville-Barnes forceps for a prolonged second stage at 41 weeks gestation. She had some vaginal bleeding early in the current pregnancy and an ultrasound scan showed a twin pregnancy. At 17 weeks gestation she presented with a history of ruptured membranes which was confirmed on speculum examination. An ultrasound scan was performed and showed twin I to have BPD, HC, AC and femur length measurements between the 40th and 50th centiles while the same measurements of twin II were on the 50th centile. The sac of twin I showed oligo-

hydramnios and a diagnosis of spontaneous rupture of membranes of this twin was made. Microscopy of a low vaginal swab demonstrated scanty pus cells and broad spectrum antibiotics were administered although culture yielded only normal regional flora. Conservative management was undertaken after discussion with the parents and 2-weekly review was arranged. Ultrasound scans at 19 and 22 weeks gestation revealed progressive reduction in the growth of twin I to <5th centile while the growth of twin II remained constant. The woman then presented at 25 weeks and 4 days with prolapse of the umbilical cord of twin I into the vagina. An ultrasound scan confirmed that twin I had died but also showed that twin II was alive and that its growth had accelerated to between the 60th and 70th centiles. She was given pethidine 75 mg and the umbilical cord, having been pulled further into the vagina, was trimmed as high in the cervix as possible. Antibiotics were prescribed. She was discharged home 24 h later feeling well but she returned the following day complaining of a lump in the vagina and shortly after admission spontaneous expulsion of the first twin occurred. Subsequent examination showed that the cervix had closed with the surviving twin still *in utero*. Ultrasonography revealed that the remaining twin had reached the 85th centile for gestational age with normal amniotic fluid volume and an estimated fetal weight of 1.2 kg at 25 weeks and 6 days. Conservative management was continued with regular vaginal swabs taken for culture and dexamethasone 24 mg in divided doses was administered after the 26th week. At 27 weeks and 5 days spontaneous rupture of the membranes of the second sac occurred. No contractions were apparent and culture of a low vaginal swab yielded normal regional flora. She remained in hospital for 2 more days when regular contractions started. The presentation was cephalic and vaginal delivery was anticipated. One hour after the contractions had commenced persistent late decelerations of the fetal heart rate occurred. Vaginal examination showed the cervix to be 8 cm dilated with a high presenting part and caesarean section was performed immediately.

The mother's initial recovery after the caesarean section was normal. She continued with the broad spectrum antibiotics but developed pyelonephritis on the second post operative day which responded to gentamicin. She was discharged 7 days after delivery.

Neonatal course. The baby, a boy, weighed 1248 g. Apgar scores were 3 and 1 minute and 7 at 10 min. He was given IPPV for 24 h and was then extubated. Antibiotic treatment with penicillin and gentamicin was commenced shortly after birth. Surface cultures grew *E. Coli* but blood cultures were negative. An unconjugated jaundice was treated with phototherapy. At 6 days of age, having started enteral feeding, he developed necrotizing enterocolitis which responded to antibiotics and parenteral nutrition. At 37 days of age he developed bronchiolitis due to respiratory syncytial virus and required IPPV and treatment with nebulized Ribavirin. Over the next few days additional inspired oxygen was gradually reduced until he was breathing air.

He was discharged home at 2 months of age and follow-up until the most recent visit at 14 months of age has not revealed any neuro-developmental problem. Subsequent admissions have, however, been necessary for the treatment of pneumonia, wheezing and a single febrile convulsion. In addition, he has had recurrent otitis media which has necessitated the insertion of grommets. It has now been established that he has a serum dependent inherited defect of complement which affects phagocytosis and killing by leukocytes. This will require long-term antibiotic therapy in childhood. His weight and head circumference are in the normal range.

Discussion

The complications of twin pregnancy and their contribution to early pregnancy loss and perinatal mortality rates are well known. Spontaneous rupture of the membranes of one sac followed by the birth of the first twin usually results in the pregnancy being terminated because of the traditional belief that a poor outcome is certain. A successful outcome for a remaining twin is, however, not uncommonly seen following the death of one twin *in utero* without membrane rupture. Death may occur early, resulting in a fetus papyraceous, or later in the pregnancy resulting in the birth of the dead twin with its live counterpart. Continuation of the pregnancy after one twin has miscarried is rare. Four cases are presented in this report where conservative management was adopted

after early spontaneous rupture of the membranes of the first sac and subsequent expulsion of the presenting fetus has occurred. In each case the pregnancy continued and the second twin survived with no discernible long-term problems that could be ascribed to the unusual circumstances which occurred in the pregnancy.

Williams & Cummings (1953) reported a twin pregnancy with one fetus in each horn of a uterus didelphys where the second twin was born 57 days after labour had resulted in the birth of the first twin at 32 weeks gestation. A similar case was reported by Dorgan & Clarke (1959) where the birth interval between twins was 21 days. Reports describing prolonged intervals between the births of twin fetuses in a normal uterus are rare. Abrams (1957) described a case where the first twin miscarried at 23 weeks gestation and the second twin was born 5 weeks later and survived. Druker *et al.* (1960), reported a case in which a fetus miscarried in an undiagnosed twin pregnancy after 18 weeks gestation and the presence of the second fetus was revealed after it was noticed that the uterus remained larger than would have been expected from a retained placenta. The second fetus was then born after spontaneous labour 65 days later. A more recent case of a first twin miscarrying at 21 weeks gestation, followed by the successful birth of the second twin at 33 weeks gestation was described by Feichtinger *et al.* (1989).

Tacchi & Dunlop (1987) reported prolapse of the umbilical cord of one of a set of triplets at 19 weeks gestation. After treatment with ritodrine and antibiotics the leading fetus was extracted under anaesthesia, the cord was excised close to the placental disc and a mersilene tape cervical suture was inserted. Surviving twins were born 9 weeks later.

The present report appears to be the largest series in which conservative management of twin pregnancy was employed after the first fetus had been expelled from the uterus. The time interval between the births of the fetuses ranged from 8 to 21 days and in each case there had been severe growth impairment of the first twin. In three of our patients this followed rupture of the membranes and development of oligohydramnios. Prophylactic antibiotics were prescribed after rupture of the membranes of the first twin to discourage the development of chorio-amnionitis which would have jeopardized the survival of the second twin.

Although the birthweight of one baby (patient

no. 3) was <3rd centile, the other three had birthweights >50th centile for their gestational age. Growth of all the surviving fetuses had been noted to be better than that of their co-twins who subsequently died. In patient 4, death of the discordantly small fetus was followed by a growth spurt in the survivor. We postulate that uterine blood flow, already increased in pregnancy, is even greater in twin pregnancy to accommodate the metabolic needs of two babies. When one twin dies, then the augmented blood flow will be available to the survivor who would consequently gain more weight than expected in the period before delivery.

A factor of great importance in the survival of the remaining twin is the availability of a neonatal intensive care unit: all the babies in our series needed specialist support. It is encouraging that all of them are neuro-developmentally normal at the time of reporting with follow-up periods ranging from 11 months to 3 years.

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Twin pregnancy in a patient with idiopathic long QT syndrome. Case report

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Case report

A 28-year-old woman (G₂P₀) presented for antenatal care at 10 weeks gestation. She had been diagnosed with long QT syndrome following a syncopal episode and cardiac arrest whilst receiving an award at a public ceremony the previous year. Following the arrest (and timely resuscitation by coincidentally present medical practitioners), she had been comatose for 2 days. Moderate memory impairment had resolved fully by her presentation for antenatal care.

She was maintained on propranolol 40 mg three times per day with no subsequent syncopal episodes. She had initially considered a home birth, but had changed her mind on the strong advice of her local medical practitioner.

At booking, aside from ECG confirmation of the diagnosis of long QT syndrome, no other abnormality was noted (Fig. 1). At a subsequent visit, the uterine size was detected to be greater than expected from her menstrual history. An ultrasound scan at 20 weeks amenorrhoea showed a twin gestation. The antenatal course was unremarkable. She was seen in close consultation with obstetric, medical and paediatric teams. The dosage and frequency of propranolol during the pregnancy remained unchanged. Ultrasonography at 29 and 35 weeks confirmed normal, concordant fetal growth. Management options were discussed with the patient by the medical team involved, and over the course of the pregnancy a plan developed.

She presented in early labour at 39 weeks gestation. The leading twin was in a deeply engaged vertex presentation. As planned, she was allowed to labour normally. A precautionary intravenous cannula was inserted, and the obstetric, medical, paediatric and anaesthetic staff alerted. Baseline ECG was performed. Electrolytes were normal. A cardiac monitor and defibrillator were readily accessible. Spontaneous rupture of membranes at 5 cm dilatation revealed lightly meconium stained amniotic fluid. Continuous fetal monitoring showed a variable and late deceleration pattern in the leading twin with a baseline of 110 beats/min, but normal variability (Fig. 2). Scalp pH was 7.31. On this basis and because of good progress, the labour was allowed to proceed and at this stage, she elected to have an epidural for pain relief. The abnormal CTG pattern persisted necessitating frequent pH estimations which ranged from 7.35 to 7.24. Labour progressed well, and 5 h after rupture of membranes, both twins were born by forceps. The dizygous twin boys weighed 2375 g and 2170 g, their Apgar scores at 1-min and at 5-min were 7 and 9, 3 and 9 respectively.

The postnatal course was uncomplicated. Both twins appear to have inherited congenital long QT syndrome. They have both been started on oral propranolol

Discussion

The long QT syndrome is a rare disorder characterized by stress provoked syncopal attacks, which usually precede or follow ventricular fibrillation (Schwartz 1975). Since the initial presentation may result in sudden death, its incidence in the community is probably underestimated.

The syndrome has been defined as a QT interval corrected for heart rate (QTc) of >0.44 s in

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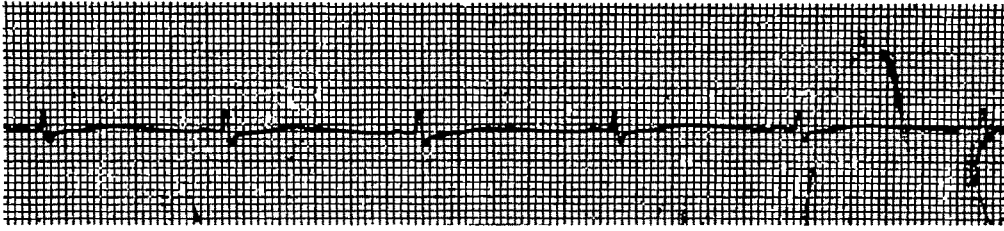


Fig. 1. Maternal electrocardiogram at bookings. Recorded at 25 mm/s, showing a QT interval of 0.52 s (13 mm)

duration (Moss 1982). Approximately 30% of cases are associated with bilateral sensorineural deafness (Jervell, Lange-Neilsen syndrome).

Extreme left sided sympathetic dominance of cardiac innervation has been described as the probable aetiological defect (Brunor 1984). Mode of inheritance has been difficult to define (Fraser 1964). The best therapeutic results are obtained by antagonizing the effects of sympathetic activity on the heart with beta blocking agents and/or by ablating the left stellate ganglion along with the first thoracic ganglion (Crampton 1978). Prophylactic beta blockage in maximal amounts tolerated has decreased mortality from 73% overall to 6% (Schwartz 1975)

The reported experience in management of pregnancy in patients with long QT syndrome is very limited. Brunor (1984) reported a normal pregnancy, spontaneous labour and forceps lift-out under epidural analgesia in a woman with long QT syndrome controlled with left stellate ganglion blockade. Ryan (1988) reported management by caesarean section of a pregnant woman affected by long QT syndrome. Gutgesell (1990) documented a normal vaginal delivery in an affected 39-year-old woman on maximal dose bretylium tosylate.

Our patient caused major concern amongst the medical and nursing staff involved. The limited obstetric experience in managing such a

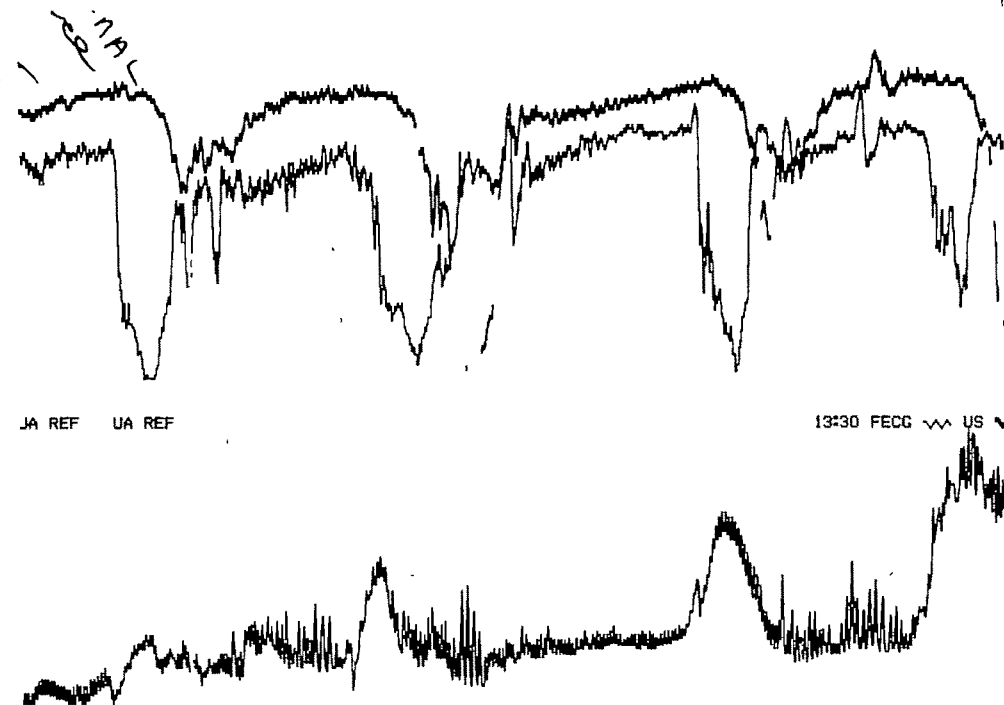


Fig. 2. Cardiotocogram during late first stage, showing simultaneous records. Twin 1 has the lower baseline and deeper decelerations.

cardiac complication was compounded by the additional physiological stresses of a twin pregnancy.

Specific problems in analyzing cardiotocographic monitoring arose. The influence of maternal beta blockade and possible impact of congenital fetal cardiac conduction defect was considered in interpretation. Resort to scalp pH estimations to refute evidence of fetal distress was justified.

Experience in cardioversion in pregnancy is also uncommon. Most reviews report good outcome, with maternal and fetal morbidity and mortality apparently relate to the maternal condition rather than the cardioversion itself (Ueland 1981).

The philosophy of a planned conservative approach with minimal intervention was considered important in this case. We reasoned that a more interventionist management would generate much of the psychological and physical stresses that we were trying to avoid.

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SHORT COMMUNICATION

Avicenna's recipe for contraception

B. Nathan, *Surgical Research Fellow, Institute of Cancer Research, Sutton, Surrey* & M. Mikhail, *GP Trainee, Brookside, Reading*

Avicenna (980–1037), the famous Persian physician and philosopher, is a figure whose writings have dominated medical thought for many centuries. *The Canon of Medicine* was his most famous book and was translated into Latin by Gerard of Cremona (d 1187). The book then went through more than 80 editions and formed an important part of the curricula of medical schools in Europe before and during the renaissance (Cooper 1930). The Canon was incompletely translated to the English language. Gruner (1930) translated Volume I based on the Latin versions published in Venice in 1595 and 1608 and the Arabic text published in Cairo in 1877.

From the Canon, we present Avicenna's views on contraception and his various recipes. It is a translation of the entire chapter on contraception (Avicenna 1877) which to our knowledge is the first English translation. It gives an idea on the diversity of the pharmacopaeia of the age and demonstrates Avicenna's understanding of the risks incurred on the urinary continence mechanism during labour. The words in parentheses are our additions to clarify the text.

"A physician may consider the prevention of pregnancy in a young (woman) if labour is feared due to an ailment in the womb. Also, if there is

weakness in the bladder, the weight of the fetus could damage the bladder causing leakage of urine and failure to maintain continence till the end of (the patient's) life. To achieve contraception factors that lead to pregnancy should be avoided. The two emissions (? orgasms) should not occur together, and (the male) should withdraw quickly. Also, after completion, the woman is asked to stand upright and to hop backwards seven or nine times as this might expel the semen. Jumping or leaping forwards on the other hand might secure the semen. Also sneezing might help expel the semen. Other measures that (the woman) might consider is to insert (vaginally) tar before and after coitus, and also to anoint the penis with tar, balsam and ceruse lead. Also to insert before and after coitus oil of pomegranate and alum. The insertion of a cabbage bud and cabbage seeds after the cessation of menstruation and before and after coitus is effective in this respect especially if dipped before in tar or menthol oil. Also insert leaves of willow mixed in equal parts of oil of colocynth, white jalap, sulphur, scammony, cabbage seed and tar. The insertion of pepper after coitus prevents pregnancy, so will the insertion of elephant's dung or using it as incense at the times stated. Three ounces of basil also if drunk will prevent conception so will the insertion of ivy leaves after the cessation of the menses."

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BLAIR BELL RESEARCH SOCIETY

Papers presented at the meeting in January 1991 at University College and Middlesex School of Medicine, London

Neonatal basal platelet intracellular free calcium concentrations in normotensive and hypertensive first pregnancies by M. D. Kilby, F. Broughton Pipkin and S. Heptinstall.* Departments of Obstetrics and Medicine, * University Hospital, Nottingham NG5 2UH.

Platelet intracellular free calcium concentration $[Ca^{2+}]_i$ controls the subcellular process of platelet aggregation and secretion. 'Paired' maternal and umbilical vein samples were taken in the *late intrapartum period* from: (i) 18 normotensive primigravidae, (ii) six primigravidae with non-proteinuric hypertension (PIH) and (iii) nine primigravidae with proteinuric hypertension. These data were compared with a control group of 30 normotensive, non-pregnant nulliparous women. Platelet $[Ca^{2+}]_i$ was measured using a Fura-2 method (assay coefficient of variance on triplicates 10.4%). In the normotensive group, the mean neonatal platelet $[Ca^{2+}]_i$ (87.9, SD 14.6 nM) was *not* significantly different from that found in the non-pregnant group (96.4, SD 17.6 nM) or in paired samples taken from the mothers 12 weeks postnatally (91.2, SD 12.9 nM), but the neonatal values were significantly different from values in maternal samples obtained at delivery (129.3, SD 14.5 nM; $P<0.001$). The 15 pregnancies with PIH (blood pressure $>140/90$ mmHg) were investigated prospectively (the diagnosis having been made in the antenatal period). Nine of these pregnancies developed proteinuria (>0.5 g/24 h). In the non-proteinuric PIH group the mean neonatal platelet $[Ca^{2+}]_i$ was 84.6 (SD 11.8) nM which was similar to the mean concentration in their mothers at 12 weeks postnatally (95.6, SD 12.7 nM, but again, there was a significant difference between the neonatal and maternal values at delivery (135.6, SD 14.6 nM; $P<0.01$). Likewise, a similar significant difference was only noted between the neonatal and maternal platelet $[Ca^{2+}]_i$ in the subgroup of primigravidae who developed pre-eclampsia in the late intrapartum

period (89.6, SD 13.7 nM vs 146.1, SD 14.9 nM; $P<0.001$). The 15 women who developed PIH had a significantly higher platelet $[Ca^{2+}]_i$ (mean 141.4, SD 18.2 nM) compared with the normotensive women of similar gestation (129.3, SD 14.5 nM; $P<0.02$). Unpaired analysis of the platelet $[Ca^{2+}]_i$ from normotensive and hypertensive umbilical cord blood has demonstrated no significant difference between the two groups. Neonatal platelets seem either refractory or protected from aetiological factor(s) causing an elevation in pregnant women, which thus reflects their relative hypoactivity.

Peri-implantation phase lectin binding in the endometrium of women with unexplained infertility by L. D. Klentzeris, J. N. Bulmer, T. C. Li, A. Warren and I. D. Cooke. University Department of Obstetrics and Gynaecology, Jessop Hospital for Women, Sheffield. Institute of Pathology, University of Leeds, Leeds.

To investigate whether the peri-implantation phase endometrium in women with unexplained infertility is, in some aspects, different from the endometrium of the normal fertile woman, five biotinylated lectins: concanavalin A (Con A), wheat germ (WGA), soyabean (SBA), peanut (PNA) and *Ulex europaeus* (UEA), were used as analytical probes for the study of endometrial glycoconjugates. Thirty six endometrial biopsies were obtained from normal fertile women (Group I) and women with unexplained infertility (Group II) at 5, 7 and 9 days following the LH surge. The lectin binding of the tissue was performed with the avidin-biotin peroxidase complex (ABC) method. In group 1, Con A stained the subnuclear glandular cytoplasm, stroma cells and surface epithelium on Day LH +5 and there was increasing staining intensity of the glandular apical cytoplasm and secretions from day LH +7 to LH +9. In group 2 the binding of the lectin to the glandular or surface epithelium was none or equivocal. In group 2, WGA stained the glandu-

lar cytoplasm and stroma cells on days LH +5 and LH +7. Luminal staining was strong on day LH +9. In Group 2 the lectin was absent from the glands but it was present in the stroma. The SBA and PNA were present in the glandular lumen of group 1 only. UEA stained vascular endothelium in both groups. In summary this study has shown that during the peri-implantation phase, the most critical time of an intrauterine pregnancy, the endometrium of women with unexplained infertility shows deficient production of glycoconjugates in the glandular and surface epithelium. A consequence of this deficiency is likely to be impairment of blastocyst implantation.

Control of fetal cardiovascular response to hypoxia by D. A. Guissani, J. A. D. Spencer, P. J. Moore and M. A. Hanson. Department of Obstetrics, University College, London WC1E 6HX.

Twelve pregnant sheep (119–126 days gestation) had instruments inserted under general anaesthesia. Catheters were placed in a carotid artery, a jugular vein and the amniotic cavity. Flow transducers (Transonic, Ithaca) were implanted around the other carotid artery and a femoral artery. Six fetuses had both carotid sinus nerves cut (denervated group) and other fetuses were left intact. On the fourth post-operative day, fetal isocapnic hypoxia was induced for one hour by a reduction in maternal FiO_2 (fraction of inspired oxygen). On subsequent days this was repeated after giving either atropine or phentolamine. The initial bradycardia and increase in femoral resistance, seen within 5 min of the onset of hypoxia in the intact group, did not occur in the denervated fetuses. The reflex bradycardia was abolished by atropine. Phentolamine infusion to intact fetuses abolished the rise in femoral resistance and all phentolamine-infused denervated fetuses died during hypoxia. We conclude that there is a carotid chemoreflex component to the initial bradycardia and increase in femoral resistance in response to hypoxia. We confirm that this reflex bradycardia is by a cholinergic mechanism. Femoral vasoconstriction during hypoxia is by an alpha-adrenergic mechanism. We believe that survival of the denervated fetuses during hypoxia was impaired by phentolamine due to blockade of catecholamine release from the adrenal gland. Since phentolamine was less deleterious to intact fetuses during hypoxia, other non alpha-adre-

nergic reflect mechanisms, such as vasopressin or angiotensin release, may be important.

The effect of donor blood haematocrit on fetal blood rheology after in utero transfusion by C. R. Welch, M. W. Rampling and C. H. Rodeck. Fetal Medicine Unit, RPMS Institute of Obstetrics & Gynaecology, Queen Charlotte's and Chelsea Hospital, London W6 0XG

We have previously demonstrated an exponential increase in fetal whole blood viscosity as haematocrit rises during in utero intravascular transfusion. We noted a concomitant change in fetal plasma proteins. We hypothesize that the change in plasma proteins was a result of protein quantity in the donor blood. We studied the effect of donor haematocrit on the change in fetal plasma protein level. The mean rise in plasma proteins over transfusion was 5.97 g/l (95% CI 2.09 to 9.84 $P = 0.007$ $n = 25$). The change in fetal plasma proteins was significantly correlated with the donor haematocrit ($y = 45.6 - 0.52x$, $P = 0.05$). We calculated the optimum donor haematocrit to avoid change in plasma protein levels should be around 88% (CI - 7.84, 7.43). Donor haematocrits above this level are associated with a dilution of fetal plasma proteins and would seem ideal in terms of minimising haemorheological changes. However, donor haematocrits above 90% are practically difficult to transfuse. Fetal whole blood viscosity changes with haematocrit and plasma viscosity. Plasma viscosity alters with fetal plasma protein levels. A large rise in fetal plasma protein level at the same time as fetal haematocrit greatly increases the whole blood viscosity and may explain acute transfusion related fetal morbidity.

Laparoscopic ovarian diathermy in the management of infertility in women with polycystic ovaries; results of treatment in 50 cases by N. A. Armar and G. C. L. Lachelin. Department of Obstetrics & Gynaecology, University College and Middlesex School of Medicine, 86–96 Chennies Mews, London WC1E 6HX

Fifty oligomenorrhoeic women with polycystic ovaries, complaining of infertility, refractory to medical treatment, underwent laparoscopic ovarian diathermy from $3\frac{1}{2}$ years to 6 months ago. Twenty one were found to have adhesions and/or endometriosis. Regular ovulatory cycles ensued in 78% and treatment with clomiphene was used successfully to induce ovulation in 7 of

the 11 non responders. Twenty six women have conceived 35 pregnancies of which 19 ended in the birth of a live healthy baby, 10 are ongoing and 6 miscarried. Seven women have conceived two pregnancies each and one has conceived three pregnancies. Only two of the women who miscarried have not had a subsequent successful pregnancy. There has been only one twin pregnancy (following clomiphene treatment) and there have been no ectopic pregnancies. Ovarian diathermy is thus a very useful option in the management of anovulatory infertility in women with polycystic ovaries.

The relation of fetal acid-base status at delivery to the cardiotocograph and T/QRS ratio by N. A. MacLachlan, K. Harding, S. Arulkumaran & J. A. D. Spencer. Queen Charlotte's and Chelsea Hospital, London W6 0XG.

Using an on-line microprocessor system (STAN, Cinventa, Gothenberg) the fetal electrocardiogram T/QRS ratio was analysed in the last 30 min of 100 labours and related to the cardiotocograph (CTG) (FIGO classification), the acid-base status of the fetus, and neonatal condition. Suspicious and pathological CTGs were associated with significantly lower median umbilical artery pH values than normal CTGs ($P < 0.03$ and $P < 0.001$ respectively), but there were no significant differences in mean T/QRS ratios. The T/QRS ratio correlated with umbilical artery pH (Spearman $P < 0.001$). Acidaemia at birth (umbilical artery pH < 7.20) was associated with a significantly higher median T/QRS ratio (0.21) compared with non-acidaemic fetuses (0.13, $P < 0.001$). Of the 100 fetuses studied, 95 were clinically normal and the median T/QRS ratio of this group was 0.14 (range 0.0–0.32, 2.5 and 97.5 percentiles 0.00 and 0.29 respectively). Five babies required admission to the neonatal

unit but none of these was clinically asphyxiated or had elevated T/QRS ratio. Of the seven fetuses with an elevated T/QRS ratio, all had a normal CTG and none required admission to the neonatal unit. Until the range of T/QRS ratio values related to clinical birth asphyxia is known, conventional management of labour using fetal heart rate and pH should not be altered.

Haemodynamics in proteinuric and non-proteinuric pregnancy induced hypertension (PIH) by S. C. Robson, S. McPhail and C. H. Rodeck. RPMS Institute of Obstetrics, Queen Charlotte's Hospital & University of Newcastle.

Varying haemodynamic results have been reported in women with PIH. We have measured cardiac output (CO) using cross-sectional and Doppler echocardiography at the aortic valve in 64 primigravidae with PIH (diastolic blood pressure ≥ 90 mm Hg), 44 of whom had proteinuria (> 0.5 g/24 h). None of the women had received antihypertensive therapy and all were delivered within 7 days of measurements because of deteriorating disease. The results were compared with 64 normotensive (NT) primigravid controls matched for age and gestation (see Table 1)

Within the proteinuric PIH group, women with more severe hypertension (DBP > 100 mm Hg, $n = 20$) had a lower CO (5.49 vs 6.60 l/min, $P < 0.01$). We conclude that PIH is associated with an increase in TPVR. Although some women with PIH have a low CO, the range of values is wide.

Fetal and neonatal condition related to epidural analgesia by J. A. D. Spencer, M. Koutsoukis and A. Lee. Queen Charlotte's & Chelsea Hospital, London W6 0XG.

Table 1. Haemodynamics in normotensive (NT) and hypertensive (PIH) pregnancy

Results:	PIH	NT	PIH + proteinuria	NT
Heart rate (beats/min)	83 (10)	80 (11)	78 (13)	84 (8)
Stroke volume (ml)	77 (15)	88 (15)	77 (17)	82 (11)
CO (l/min)	6.43 (1.36)	7.01 (1.47)	6.06 (1.53)	6.83 (0.91)
MAP (mm Hg)	109 (6)**	89 (8)	116 (10)**	85 (8)
TPVR (dyne s/cm ⁻⁵)	1418 (350)**	1054 (269)	1626 (590)**	1016 (171)

Results are mean (SD) values, MAP = mean arterial pressure, TPVR = total peripheral vascular resistance
* $P < 0.01$, ** $P < 0.001$ vs NT)

In a prospective study of 200 labours reaching the second stage, epidural rates were representative of our overall figures: primiparae 52%, multiparae 18% (odds ratio 5.0, $P < 0.001$); normal vaginal delivery 21%, operative vaginal delivery 77% (odds ratio 12.6, $P < 0.001$). Meconium staining of amniotic fluid (incidence 15%) was not related to epidural analgesia. Fetal blood sampling (FBS) in the first stage of labour was performed in 8% of labours, 67% of which had an epidural compared with 34% of labours not requiring an FBS (odds ratio 3.9, $P < 0.02$). In the hour preceding the second stage, 25% of labours showed variable or late decelerations of the fetal heart rate (FHR), 67% of which had an epidural compared with 32% in those with early or no decelerations (odds ratio 4.5, $P < 0.001$). Late or variable decelerations occurred in 50% of labours during pushing and epidurals had been used in 48% compared with 30% in labours where decelerations were early or absent (odds ratio 2.1, $P < 0.02$). The 1-min Apgar score was < 7 in 12% of the newborn and the use of epidural during these labours was 56% compared with 34% in the remaining labours (odds ratio 2.8, $P < 0.02$). This may be related to the number of forceps delivery. Only one infant had a 5-min Apgar score of < 7 . Umbilical artery acidemia (pH < 7.12) was present in 15% of labours, 47% of which had an epidural compared with 36% of those without this degree of acidemia. FHR decelerations were associated with epidural analgesia but umbilical artery acidemia was not, indicating that such reflex FHR changes are not indicative of fetal distress.

Serum lipid and lipoprotein concentrations in polycystic ovary disease by R. Fox, E. Corrigan, C. Coulson and M. G. R. Hull. University Department of Obstetrics and Gynaecology, Bristol Maternity Hospital.

Insulin resistance is a common feature of both obese and non-obese women with polycystic ovary disease (PCOD). Euglycaemia is maintained by a compensatory rise in insulin levels. Lipid status has not been studied in detail. Insulin, fructosamine, triglyceride, total cholesterol and high density lipoprotein cholesterol (HDL-cholesterol) were measured after a 10-h fast in 46 anovulatory women with PCOD and 30 non-obese ovulatory controls. The data are expressed as mean (SD) or median (range) values. The PCOD group had similar fructosamine levels to the controls (2.2 (0.3) vs 2.2 (0.2)

nmol/l, $P = 0.44$), despite having higher concentrations of insulin (18 (3–85) vs 5 (3–14) u/l, $P < 0.001$). In addition, they had higher triglyceride concentrations (1.3 (0.5–4.7) vs 0.8 (0.4–1.5)) nmol/l, $P < 0.001$ and total cholesterol: HDL-cholesterol ratios (4.0 (2.0–9.6) vs 3.7 (2.4–5.1), $P < 0.001$). Overall, 26 (57%) of the women with PCOD and 3 (10%) of the controls had at least one abnormal lipid result ($\chi^2 = 15.4$, $P < 0.001$). Triglyceride results were significantly correlated with body mass index (BMI) ($r = 0.69$, $P < 0.001$) and insulin ($r = 0.63$, $P < 0.001$). HDL-cholesterol levels were negatively correlated with fructosamine/E₂ ratio ($r = -0.31$, $P = 0.047$). Non-obese women had lower levels of HDL-cholesterol ($P = 0.047$) and higher levels of triglycerides ($P = 0.043$) than controls. Both obese and non obese PCOD patients had evidence of hyperlipidaemia. Triglyceride was related to BMI and/or insulin but the reduction in HDL-cholesterol concentrations was related to sex steroid levels.

Consumers' views of the maternity services: implications for medical audit and planning by R. J. W. Melia, A. V. Swan, M. Morgan and C. D. A. Wolfe. Department of Public Health Medicine, UMDS of Guys and St Thomas' Hospitals, St Thomas' Campus, London.

The usefulness and feasibility of consumer surveys for medical audit and planning maternity services were assessed in a postal survey of 1807 women in four health districts covering rural and urban/deprived areas. A response rate of 79% was achieved. Scope was identified for some reduction in length of stay: 28% of antenatal and 43% of postnatal women wished for a shorter stay than expected or experienced. The Domino system and a 1–2 days stay were the preferred options (25 and 24% respectively). A small group of women ($< 10\%$) would have preferred a longer stay and consisted mainly of women with birth complications including abdominal deliveries, women with lack of help at home, and Afro-Caribbeans. Schemes to increase continuity of care and make the delivery suite more home-like would be favoured by a large proportion of women. Overall 65% of the women regarded continuity of midwifery care and familiarity with the delivery midwife as important. More than 75% reported a home-like environment in the delivery suite as important and gave specific suggestions of how this might be achieved. The results show that consumers' sur-

veys are feasible with a good response rate and range of views expressed by the study population, and they provide guidance for planning at local and regional levels.

Stable isotope studies of albumin synthesis during normal pregnancy by O. S. Olufemi, T. Lind, P. G. Whittaker and D. Halliday*. University Department of Obstetrics & Gynaecology, Princess Mary Maternity Hospital Newcastle, Tyne & Wear and *Nutrition Research Group, MRC Clinical Research Centre, Harrow, Middlesex.

Our serial studies of 69 normal women have shown that maternal plasma protein concentration decreases during pregnancy, largely due to a 22% decrease in albumin concentration. However, after allowing for the 53% increase in plasma volume, the total amount of circulating albumin increases by about 19% suggesting a change in metabolism. Determination of albumin synthesis using stable isotopes has previously used a 60 h oral feeding method. We have developed a new protocol (with ethical approval) in five non-pregnant subjects using a primed, constant infusion of ^{15}N -glycine together with priming of the urea pool. Enrichment of ^{15}N arginine in albumin together with ^{15}N enrichment in urinary urea (measured by an isotope ratio-mass spectrometer, IR-MS) has been used to compute albumin fractional synthetic rate (FSR) over a short period (12 h) as well as providing data concerning protein turnover. Simultaneous infusion (8 h) of ^{13}C -leucine in the same subjects (measuring ^{13}C -leucine in albumin by IRMS and ^{13}C -keto-isocaproate by gas chromatograph-MS) and thereby determining albumin synthesis independently allowed us to validate the latter method. The two estimates of FSR (by ^{15}N -glycine: mean 0.255 (SD 0.038)% h, by ^{13}C -leucine: mean 0.252 (SD 0.044)% h agree with each other despite the different assumptions inherent in both methods. The above protocols were also performed in five

pregnant subjects at 36 weeks gestation and showed that FSR (by ^{15}N -glycine: mean 0.303 (SD 0.083)% h, by ^{13}C -leucine: mean 0.318 (SD 0.085)% h, is higher at the third trimester of pregnancy, thus supporting the hypothesis of an alteration in albumin metabolism during pregnancy. This work was supported by Birthright.

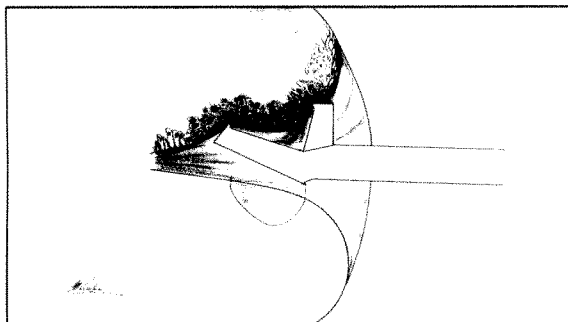
Microalbuminuria in pregnancy induced hypertension by K. J. Thong, F. Howie, * A. F. Smith, I. Greer and F. D. Johnstone. Department of Obstetrics, Simpson Memorial Maternity Pavilion, and Department of Clinical Chemistry*.

Current controversy in pregnancy induced hypertension (PIH) centres on whether there is a spectrum of disease activity or whether there are two separate conditions, proteinuric and non proteinuric hypertension with different outcomes. The aim of this study was to clarify one of these issues in PIH by measuring the albumin/creatinine ratio. A total of 162 primigravida was included in this study. These patients were classified retrospectively and comprised 72 non proteinuric PIH, 27 proteinuric PIH and 63 normotensive women. A daytime midstream urine sample was collected from all the women but in the PIH group, urine was collected at the time of diagnosis. Urine albumin concentration was measured using a turbidmetric method and the urine creatinine measured by a standard Jaffe method on the Cobas Fara centrifugal analyser. The three clinical categories can be clearly separated on the basis of the albumin/creatinine ratio ($P < 0.00001$ for all comparisons). The geometric mean and the 95% range were: normal (1.23; 0.32–4.8) proteinuric PIH (13.8; 0.96–198.2) and non proteinuric PIH (2.22; 0.34–14.7) respectively. This study demonstrated a spectrum of disease activity in PIH from the absence of microalbuminuria to gross proteinuria. The finding that 29% of non proteinuric PIH patients had significant microalbuminuria is against the concept of 2 separate conditions, that is proteinuric and non proteinuric.

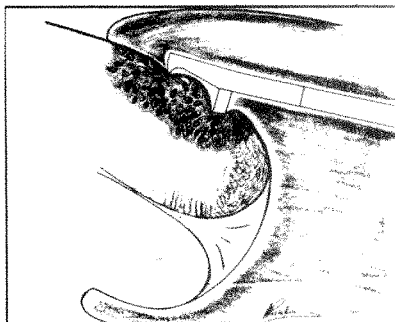
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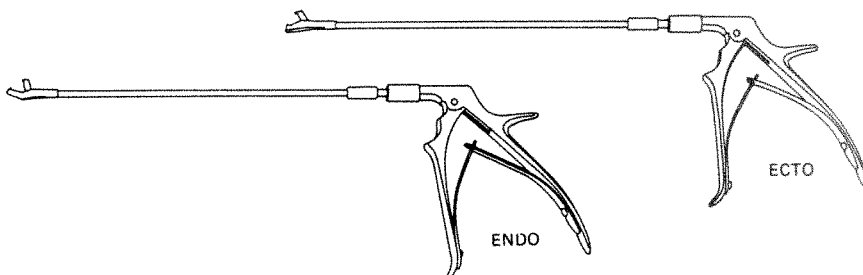


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J. T. E. Richardson, Brunel University, Uxbridge, UK (Ed.)

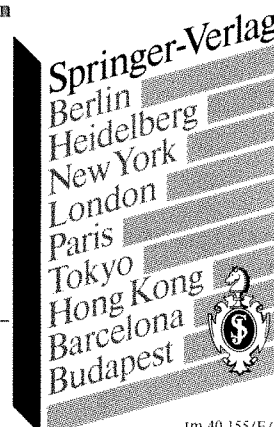
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CORRESPONDENCE

Management of tubal infertility in the 1990s. Commentary

Dear Sir,

The commentary by Reiss [*Br J Obstet Gynecol* (1991) 98, 619–623] states that it seems unlikely that laparoscopic tubal surgery will replace open microsurgery except in the hands of a few enthusiasts when used for the most favourable of cases. It is also stated that laparoscopic tubal surgery carries with it a higher complication rate than laparotomy although this was not discussed in detail. This technique is stated as being more time consuming and expensive, and of having limited success. We believe that minimally invasive techniques will play an important role in the management of tubal infertility.

Ovanolysis, salpingolysis, ovario-salpingolysis, fimbrioplasty and salpingostomy have become well established laparoscopic procedures. Gomel (1977) reported a 44% intra-uterine pregnancy rate after laparoscopic salpingostomy, with a 90% postoperative tubal patency rate for at least one tube and no extra-uterine pregnancies; in contrast, only 27% achieved viable pregnancies after microsurgical salpingostomy by the same operator (Gomel 1978). Although the laparoscopic results have been bettered (Manhes 1987), most of the more recent and larger series are still achieving pregnancy rates of 26–28.5% (Mettler *et al.* 1979; Reich 1987) after conventional laparoscopic salpingostomy, and 20–25% (Daniell & Herbert 1984; Donnez & Misolle 1989) if a laser is used. As with open microsurgery, results are even better with lesser degrees of tubal damage. Fimbrioplasty has been shown to produce pregnancy rates of 31–61% (Mettler *et al.* 1979; Donnez & Misolle 1989), and salpingo-ovariolysis 58–78% (Reich 1987; Donnez & Misolle 1989). Laparoscopic techniques can also be used to treat other major causes of infertility such as severe endometriosis and clomiphene resistant polycystic ovarian syndrome, with pregnancy rates of 67.2–80% (Nezhat *et al.* 1989; Gjönnæss 1984).

Adhesion formation is a significant aetiological factor in tubal infertility, and appears to be less when the abdomen is not opened (Bruhat *et al.* 1983), which is a major advantage of the laparoscopic approach.

Ectopic pregnancy is an important risk after any form of tubal surgery, not only as a result of the surgery itself but also as a consequence of the underlying tubal damage. The approach would appear immaterial with extra-uterine pregnancy rates of 2–18% following tubal microsurgery and 5–16% after laparoscopy (Cohen 1988).

Laparoscopic surgery is no more time consuming than open surgery, although we accept that a learning curve exists, as for any new procedure, which will initially increase operating time. The average operating times for the more commonly performed laparoscopic procedures in our unit are as follows: adhesiolysis, 47 min; ovarian cystectomy, 46 min; salpingostomy with or without adhesiolysis, 58 min; ovarian cystectomy plus adhesiolysis, 52 min; and electrodiathermy to endometriosis, 44 min. These figures include time taken for demonstration and teaching and have not been adjusted for this.

We would like to see evidence for the view that complications from laparoscopy are more frequent than from laparotomy. To our knowledge the two approaches have never been compared directly. One large audit reported a major complication rate for operative laparoscopy of only 3.8/1000 (Riedel *et al.* 1986) which we would suspect is far less than for laparotomy.

As for costs, there can be no argument that day-case laparoscopic surgery is cheaper than conventional microsurgery. In an audit of 21 patients who underwent pelviscopic procedures including adhesiolysis and salpingostomy, Levine (1985) reported 79% reduction in the cost of drugs and other medical supplies, 69% reduction in the length of postoperative hospitalization, and 49% reduction in overall hospital costs. Advantages to the patient include faster recovery, reduced discomfort and, not least, less disfigurement. We would also argue that several

attempts at IVF required by most couples in view of the poor success rate of a single attempt make it a more expensive and less convenient alternative to laparoscopic surgery.

As in other areas, the role of laparoscopic surgery is expanding. It would be ironic if gynaecologists, who after all were the modern day pioneers in laparoscopy, failed to exploit the full potential of this technique. Laparoscopic surgery should become the operative route of choice for most extra-uterine pathology.

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Author's reply

Dear Sir,

I welcome the comments made by Broadbent & Magos, but must point out that my remarks about laparoscopic surgery referred only to the treatment of distal tubal disease. I have for many years advocated laparoscopic surgery for ectopic pregnancy and polycystic ovarian disease and in fact demonstrated my technique of laparoscopic ovarian wedge resection in 1987 in the hospital where they are now working. Of their references 5 of the 8 articles relating to distal tubal occlusion were quoted in my Commentary (Reiss 1991). These are precisely the laparoscopic enthusiasts to whom I referred: some of them I am proud to know as friends. The fact remains that their papers include little detail about selection criteria, and their numbers are still small, compared with the large series from Hammersmith (Winston & Margara 1991) and Sheffield (Singhal *et al.* 1991) in the same issue of the Journal. There is no concrete evidence of improved results with laparoscopic surgery since the review by Bateman *et al.* (1987).

The risks of laparoscopy are well known. Few of us publish our complications, but the records of the medical defence societies, unfortunately but for obvious reasons confidential, bear witness to the dangers. Few who like myself have practised laparoscopy for over 20 years can have escaped without some serious mishaps.

My comments were on tubal infertility management in the 1990s. Whether by the year 2000 laparoscopic surgery will have replaced open surgery for distal tubal occlusion, or be dismissed as 'laparoscopic gymnastics' remains to be seen. I made a plea for better funding and better training of infertility surgeons. Comparison of results in this field will never be possible without proper classification of tubal disease, agreed selection criteria and protocols of surgical techniques (magnification, lasers, adjuvants, prostheses, etc). I sincerely hope that members of the British Society of Gynaecological Endoscopists will join their colleagues in the British Fertility Society in jointly addressing these problems.

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British Journal of Obstetrics and Gynaecology
 December 1991, Vol. 98, pp. 1311-1312

Difficulties in the diagnosis of congenital toxoplasmosis by cordocentesis

Dear Sir,

We were very interested to read the case report by Holliman *et al.* [*Br J Obstet Gynaecol* (1991) **98**, 832-834] demonstrating again the problems of confident antenatal diagnosis of congenital toxoplasmosis.

We would like to know which serological studies confirmed acute toxoplasma infection in a woman for whom the time of seroconversion was unknown.

High titres of specific IgM persist for many years following primary infection (Fuccillo *et al.* 1987). Sever (1990) argues that toxoplasmosis screening in pregnancy is therefore of little clinical value.

The patient described underwent amniocentesis (with a risk of fetal loss of 0.5-1%) and cordocentesis with a risk of fetal loss of 2-3% (Daffos *et al.* 1985; MacKenzie *et al.* 1991), whilst the risk of fetal infection in primary maternal toxoplasmosis is thought to be between 1.5 and 6.0% (Desmonts *et al.* 1985). Some units perform cordocentesis only if antenatal seroconversion is demonstrated (Desmonts *et al.* 1985).

Cordocentesis is still a subspecialist investigation and it is unlikely that it can be offered to all patients with a positive toxoplasma titre and a history of flu-like illness in pregnancy. If a definite diagnosis of congenital toxoplasmosis cannot be reached the pregnant woman will be left with a high level of stress and the obstetrician with the decision if he should give potentially harmful, prophylactic medication.

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Author's reply

Dear Sir,

The definitive diagnosis of acute toxoplasmosis is based on the demonstration of seroconversion in two closely spaced blood samples. In the absence of a routine screening programme such samples are rarely made available and additional

techniques are required to estimate the duration of toxoplasma infection. Measurement of specific IgG avidity and IgA have been promoted for this purpose but there is insufficient experience of these indices to be of clinical value. In our laboratory, semi-quantitative IgM estimation is performed using two assays of differing sensitivity. In our experience the u-chain capture ELISA will detect specific IgM for 6 months after acute infection whilst ISAGA remain reactive for 18 months (on average). In addition, IgG levels assessed by the dye test rise during the first weeks of infection and are stable by two months (Holliman & Johnson 1991). The patient described was found to have specific IgM detected by ELISA and ISAGA and a constant level of IgG. Typically this pattern of results is recorded in a patient infected for 1–6 months duration. As the patient was at 17 weeks gestation when first examined and earlier sera were not available, the estimated risk of fetal infection was thought to exceed the risk of cordocentesis and amniocentesis.

It should be emphasized that the duration of IgM reactivity will vary with the sensitivity of the specific assay utilized as well as the individual's immune response. Consequently, improved methods for dating toxoplasma infection accu-

rately are required. Finally, it cannot be assumed that the risk of congenital toxoplasmosis is confined to cases of primary maternal infection acquired during pregnancy. Although the risk associated with pre-conceptual maternal infection is likely to be small, subsequent congenital infection has been reported (Desmonts *et al.* 1990). In view of these difficulties routine antenatal screening for toxoplasma is not recommended in the United Kingdom and only the fully counselled well/worried woman or the clinically ill should be investigated outside of the formal, ethically approved, scientific studies.

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British Journal of Obstetrics and Gynaecology
December 1991, Vol. 98, pp 1312–1313

Psychiatric morbidity and acceptability following medical and surgical methods of induced abortion

Dear Sir,

I read with interest the paper by Urquhart & Templeton [*Br J Obstet Gynecol* (1991) **98**, 396–399] on the acceptability of medical termination (mifepristone and prostaglandin). As stated by the authors, it is necessary to establish whether the new method is as acceptable to women as the surgical method. However, I would like to make a few comments. In their short review of the literature, the authors quote various studies that have been reported in the past 20 years. These suggested that therapeutic abortion is indeed beneficial to women. Most workers agree that only 10% of women are likely to develop a 'new' psychiatric illness following the abortion. However, the authors fail to point out the number of

methodological flaws in these studies: insufficient numbers, no clear description of the sample and inadequate measuring instruments (Zolese 1991). Because of these problems the figure of 10% is most likely to be inaccurate.

I am investigating the psychological sequelae of therapeutic abortion by both vacuum aspiration and mifepristone with prostaglandin. All women are assessed by the same psychiatrist with a semi-structured psychiatric interview the Schedule for Affective Disorders and Schizophrenia (Endicott & Spitzer 1978) and by the Hospital Anxiety and Depression Scale (Zigmond & Snaith 1983). A preliminary analysis of the data shows that of 84 women undergoing a surgical termination, 65% were psychiatrically ill at presentation and, at a mean follow-up time of three weeks, the number dropped to 28.3% (McNemar's $U = 3.67$, $P = 0.001$). Of a similar random sample of 45 women (recruitment not

completed) undergoing medical termination, 65.7% were psychiatric cases at presentation and 31.5% were still psychiatrically ill after a mean follow-up time of three weeks (McNemar's $U = 2.4$, $P = 0.02$).[~]

These figures are much higher than those found by Urquhart & Templeton and this might be due to the fact that their subjects were only assessed by a modified questionnaire.

Whereas termination appears to be indeed 'therapeutic' as indicated by the drop in psychiatric morbidity before and after either procedure, the number of women who remain distressed following the termination is certainly higher than 10%.

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Authors' reply

Dear Sir,

Dr Zolese is right to tell us of her work at this

stage and we look forward to seeing the completed study published in due course. Although there are methodological problems with published material, we think it is generally accepted that induced abortion does not usually cause major psychiatric or psychological problems in previously normal women. One of the difficulties lies in the definitions used, and this, assuming the populations of women in Aberdeen and London are not substantially different, must account for the difference in the incidence of problems between the two studies. I think most clinicians would be astonished to learn that 65% of women seeking termination were psychiatrically ill, although they would acknowledge that the majority of women were distressed by their predicament and deeply concerned about the abortion.

The point of our study was to show that women were no more distressed by medical abortion than by surgery, and it does seem that Dr Zolese's work might support this general conclusion. However, one of the main methodological problems with our study (freely admitted in the paper), and also it seems with the London study, is that the women were not randomly allocated to the abortion method. We have now addressed this particular difficulty in a large scale study, using a Brewin-Bradley type design, in which we have assessed the efficacy, acceptability and sequelae of medically induced abortion.

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British Journal of Obstetrics and Gynaecology

December 1991, Vol 98, pp. 1313-1314

Pre-eclampsia and anti-phospholipid antibody

Dear Sir,

The recent paper by Taylor *et al.* [*Br J Obstet Gynaecol* (1991) **98**, 604-606] merits further comment. Although the authors kindly acknowledged our *Lancet* letter (Kilpatrick *et al.* 1989) and referred to the main point of that communication, they omitted to mention that our

laboratory findings are very similar to theirs (and we tested more than twice their number of samples.)

We found that all of 52 serum samples taken from women experiencing pre-eclampsia were within our normal range for cardiolipin antibodies of IgG class (aCL), the latter being defined as the mean plus 4SD of a healthy population. This cut-off level corresponds to 14 GPL

(Chancellor *et al.* 1991). It can be calculated from the data in the Table by Taylor *et al.* that the mean value of their 20 control sera was 6.3 (SD 1.8); therefore their mean plus $\pm$ SD equals 13.5 GPL. All 20 of their pre-eclamptic sera (5.5 $\pm$ 2.3) were also within that range. Faux *et al.* (1989), while using a cut-off level which cannot be directly compared, also found no difference between pre-eclampsics and controls. Even Branch *et al.* (1989), quoted as finding cardiolipin antibodies in one-third of patients with early-onset pre-eclampsia, found aCL in only 16% of their total group of patients. Therefore, with good agreement from four independent laboratories, we can conclude with some confidence that aCL are very much a minority occurrence in pre-eclampsia.

The converse, however, may be different. Indeed, in a retrospective study of a small group of parous women with aCL, a high incidence of pre-eclampsia in first pregnancy was noted (Kilpatrick & Liston, unpublished observations). This is analogous to the observation that while aCL occur in only a small minority of women with recurrent miscarriage, women with aCL often have recurrent miscarriages.

While much work remains to be done to elucidate the significance of an individual finding of raised aCL during pregnancy, I suggest the following approach is sensible at the present time.

- (1) No action beyond continued observation should be taken with so-called low positives (GPL 5–14). values within that range are not rare in unselected, healthy populations, and the clinical significance, if any, is unknown.
- (2) Definitely positive values (>14 GPL) are abnormal, but their significance depends on whether they occur in association with a recent or concurrent infection. In particular,

HIV infection should be considered and excluded (Maclean *et al.* 1990). There is no evidence that infection-associated aCL are connected with a thrombotic tendency or poor obstetric prospects.

- (3) Infection-independent aCL levels above 14 GPL in pregnancy indicate empirical treatment with low dose aspirin, unless the patient is to be entered into a clinical trial.

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British Journal of Obstetrics and Gynaecology
December 1991, Vol. 98, pp. 1314–1315

Intrauterine pressures in labours induced by amniotomy and oxytocin or vaginal prostaglandin gel, compared with spontaneous labour

Dear Sir,

In the study reported by Lamont *et al.* [*Br J Obstet Gynaecol* (1991) **98**, 441–447] 21 of 43 women in the trial (prostaglandin) group were unavailable for analysis in this study. Some

investigators confronted with such a high rate of attrition might have redesigned their trial. Instead these investigators use the small residual number of women available for analysis to suggest that PGE₂ might have advantages over amniotomy and oxytocin because of some presumed effect on cervical resistance leading to a pattern of uterine activity closer to that of spontaneous labour.

A more practical interpretation might be that PGE₂ induction, compared with amniotomy and oxytocin in women with favourable cervixes, leads to a prolonged mean induction delivery interval (nulliparae 9.5 h vs 7.5 h, multiparae 6.0 h vs 5.1 h). These interval differences would have been ever greater if the seven women who failed to establish in labour after 12 h of PGE₂ treatment had not been excluded from analysis.

There was also a tripling of the caesarean section rate in the PGE₂ group, which provokes no comment from the authors (PGE₂ 7/43, 16% vs amniotomy/oxytocin 2/41, 5%).

It is difficult to accept their conclusion that 'our data also support the claim that labour induced with prostaglandins is as efficient, if not more so, than the traditional method of amniotomy and oxytocin'.

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Author's reply

Dear Sir,

Thank you for giving me the opportunity to reply to Mr Fraser's letter. The study was conducted under a Clinical Trials Exemption Certificate before the prostaglandin E₂ gel was commercially available. Due to the unfamiliarity of the agent, there were cases in the early part of the study when artificial rupture of the membranes (ARM) was carried out too early, but in retrospect, more gel should have been given. When labour did not ensue, oxytocin was started 4 h later in violation of the protocol. Four of these women were subsequently delivered by caesarean section and these account for the excess of

caesarean sections in the PGE₂ gel group. We now know that it is not ideal to combine prostaglandins with oxytocin.

With more experience of the gel, further small doses of gel were given rather than carry out an ARM and when no oxytocin was given, there were no further caesarean sections in this group. As stated in Table 1, there were also technical difficulties in measuring intrauterine pressure extra-amniotically, but after due consideration and critical refereeing this bias was not thought to affect the findings of the study and this was stated in the discussion.

It is quite clear that induction with PGE₂ gel leads to a prolonged induction-delivery interval of about 2 h in nulliparae and 1 h in multiparae. This delay is mainly due to a prolonged pre-established phase but results in a shorter established phase of labour.

I would surmise that the pre-established phase of labour is an important part of the first stage of labour which is virtually omitted by the use of oxytocin. During this pre-established phase, there are changes occurring within the collagen matrix, ground substance and water content of the cervix which increase compliance and decrease resistance. These changes may not manifest themselves as dilatation or shortening of the cervix. The result of this is quicker progress during the more painful, established phase of labour. Under these circumstances, some women might prefer a slightly longer labour if most of this was spent feeling niggles and back-ache during the pre-established phase.

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British Journal of Obstetrics and Gynaecology

December 1991, Vol. 98, pp. 1315-1316

'Nuns, virgins and spinsters'. Rigoni-Stern and cervical cancer revisited

Dear Sir,

The burial of a medical myth by Mr Griffiths [*Br J Obstet Gynaecol* (1991) **98**, 797-802] was most welcome. Hopefully this event will not go

unnoticed by all workers performing cervical smears, including those based in genitourinary medicine clinics. The perception of an abnormal smear as a sexually acquired infection may have deleterious psychological and physical consequences for patients.

Given the adoption of an automatic recall

system, the value (if any) of interval cytology in women attending genitourinary medicine clinics needs to be clarified. Particular problems in genitourinary medicine clinic attenders are high default rates, genital infections obscuring the cytological picture and concerns for patient confidentiality (which may be compromised if the patient defaults from follow-up). On the other hand, some women understandably prefer their smears to be taken in a genitourinary medicine clinic.

Perhaps follow-up cervical smears should only be taken in genitourinary medicine clinics when this is preferred by the patient, or when her needs cannot be met by the recall system.

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British Journal of Obstetrics and Gynaecology
December 1991, Vol. 98, p. 1316

The use of Histoacryl for episiotomy repair

Dear Sir,

How disappointing to read the report by Adoni & Anteby [*Br J Obstet Gynaecol* (1991) **98**, 476–478] that compared a tissue adhesive applied to the skin with skin stitches of 00-chromic catgut. It is hardly ever necessary to place stitches through the skin when repairing an episiotomy. A subcuticular closure obviates the placement of any stitches in the skin. I hope there will be a further report by these authors that compares results of episiotomy repair achieved by a tissue adhesive with that achieved by subcuticular closure. Such a future study should use a finer suture than 00 and one that has less potential than catgut for tissue reaction. Pain from an episiotomy has an important deep component. I look forward to a future report that describes an

adhesive, or some other technological wonder, to replace sutures for the closure of the deep portions of the episiotomy.

This is a personal communication of the author not to be construed as representing in any way either the Southern California Permanente Medical Group or Kaiser Permanente.

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References

- Adoni A. & Anteby E. (1991) The use of Histoacryl for episiotomy repair. *Br J Obstet Gynaecol* **98**, 476–478

BOOK REVIEWS

Textbook of Gynecologic Oncology edited by G. R. P. Blackledge, J. A. Jordan & H. M. Shingleton. W. B. Saunders Co. Ltd, London, Philadelphia, 1991, 504 pages, with figures and tables, £60.00

The increasing interest in gynaecological cancer from both a therapeutic and research perspective makes the appearance of a new textbook on this subject quite timely. One of the attractions of this book is an authoritative authorship from both sides of the Atlantic which provides a broad viewpoint. The editors represent the medical schools of Birmingham, Alabama and Birmingham, West Midlands but the contributors comprise many acknowledged experts from the United States, the United Kingdom and the Netherlands. The other attractive feature of the book is its division into two sections; the first quarter dealing with the principles of gynaecological oncology and the remainder of the book dealing with specific aspects of each tumour site.

For those attempting to gain further insight into gynaecological cancer the initial section is very worthwhile, dealing with general aspects of epidemiology, histopathology, cytology, staging as well as the principles of treatment and clinical trials. More on the molecular biology of cancer would be a welcome addition for any further edition. The text dealing specifically with the individual tumour sites is methodically set out with a group of chapters dealing sequentially with the aetiology and epidemiology, pathology and treatment of each tumour type. This approach provides a breadth of information which succeeds in maintaining interest throughout. The contributions in pathology in particular are excellent and well illustrated. The vital role of palliative medicine for women with gynaecological cancer is acknowledged with a chapter on the hospice approach, an aspect which has only recently won its rightful place in textbooks on cancer.

The book is generally well written, concise and very informative. Although comprehensive it is very compact and reasonably priced. It should be a valuable addition to the bookshelf of

those in postgraduate training as well as established clinicians, generalists and subspecialists alike.

H. C. Kitchener

A Colour Atlas of Childbirth and Obstetric Techniques edited by Farook Al-Azzawi. Wolfe Publishing Ltd, London, 1991, 144 pages, with figures and tables, £19.50.

Here is an addition to the popular series of Wolfe Atlases, giving colourful descriptions of common obstetric procedures. These include illustrated definitions of antenatal procedures, normal delivery, forceps delivery and rotation, the delivery of breech presentation and of twins, and Caesarean section, with an interesting addendum on *en caule* delivery by J. F. Pearson.

Each section is self-contained, which makes for easy reading when looking for a particular technique but is somewhat repetitive when reading the book as a whole.

The author rightly points out that procedures are much better understood when illustrated by a sequential series of pictures and this atlas largely meets this need, although clarity is sometimes lacking especially in the detail of suturing techniques which might be better illustrated with good drawings.

The descriptions of techniques are written in a clear and direct style, but for some readers the lack of detail may be disappointing such as an incomplete description of the Lovset manoeuvre.

Who will find this Atlas most useful? Undoubtedly medical students and student midwives will benefit by reference to the book in the delivery unit to get a preview of techniques that are likely to occur. For over 50% of medical students the step by step account of breech delivery may be the nearest they will get to the real thing but it is likely to stay in their minds should they ever in emergency be called upon to deliver a breech. For the postgraduate trainee, because of the patchy nature of the detailed descriptions only parts of the book will prove of benefit. All those conducting tutorials will find it useful to have by their side.

This is a useful book to have around the delivery unit or seminar room rather than in the library or on one's personal bookshelf. It might be argued that video cassettes would provide a better medium, especially as many delivery units now have facilities for showing them. Will this become the preferred option for the future?

B. M. Hibbard

A Practical Guide to Chorion Villus Sampling edited by David T. Y. Liu. Oxford University Press, Oxford, 1991, 115 pages, with figures and tables, £15.00

This book has been produced by David Liu and his colleagues in related disciplines, many of whom he works with in Nottingham, for obstetricians intending to set up a chorion villus sampling clinic, and for others involved in the care of women considering CVS. Its stated objective is to provide an historical view of the development of chorion villus sampling, together with its relevance to present day genetic knowledge and obstetric practice, and provide information about the practical techniques of CVS as used by the contributors to the book.

The book largely achieves its aims. There are two very good, if somewhat complex chapters providing fundamental knowledge on the principles of genetic counselling, Mendelian inheritance and DNA technology relevant prenatal diagnosis using villus material. There are two chapters discussing the interpretation of cytogenetic analyses where unfortunately there is a certain amount of duplication; compared with the two chapters on genetic counselling and DNA analyses these are relatively superficial. The role of ultrasound in early prenatal diagnosis is discussed in two chapters, again with some inevitable overlap which suggests that a single chapter might have been sufficient. The line drawings used to explain the ultrasound pictures are extremely helpful and could have been used even more frequently in the chapters describing the transcervical and transabdominal approaches to villus sampling. These two chapters provide considerable detail about the techniques used by the two authors, although the chapter on transcervical sampling could have provided slightly more technical detail, while that on transabdominal sampling is very didactic and concentrates largely upon the technique preferred by the author, dismissing other techniques.

Prenatal diagnosis is a growth industry, and

one of the most rapidly changing aspects of obstetric practice. Thus, the lag time between writing and publication must be short to avoid being out of date; David Liu has achieved this with the bibliographies for a number of the chapters including papers published in the last two years. It would, however, have been helpful to have had more facts and figures with regard to the morbidity associated with chorion villus sampling, particularly when compared with amniocentesis. The consumer, and thus those involved in advising, need to know what the latest figures are for risks of miscarriage, premature rupture of the membranes and preterm labour and the like, to enable the wisest decision to be reached. Although information on this aspect of CVS is continually being gathered, the results of the large uncontrolled study from the USA and the randomized controlled trial from Canada were published in time to be incorporated into the text and would have provided a greater insight into relative risks.

I am sure this book will be of value to obstetricians in training, family practitioners and midwives who are often the first professionals approached by couples enquiring about prenatal diagnosis. I suspect the obstetrician planning to set up a CVS clinic, however, would obtain most knowledge and experience from attending others already providing a chorion villus sampling service, and the book will probably have less interest for such specialists.

Ian MacKenzie

The Embryo: Normal and Abnormal Development and Growth edited Michael Chapman, Geddis Grudzinskas & Tim Chard. Springer-Verlag, London, Heidelberg, 1991, 263 pages with figures and tables, £60.00.

The editors and contributors of this timely book are to be congratulated on their efforts.

New developments in assisted reproduction and antenatal diagnosis have opened major new areas for research, and the two interests are combined in exploring the possibilities of pre-implantation diagnosis. There are also exciting discoveries in early pregnancy endocrinology and the endometrial proteins.

Among the many interesting contributions I was impressed by Braude and colleagues succinct chapter on Mechanisms of Early Embryonic Loss, Bolton on Embryo Biopsy, Reece and Hobbins on Embryoscopy and West on Sexing the Pre-embryo. Indeed, the illustrations of

embryoscopy and the superb series of photomicrographs on detection systems for the Y-chromosome almost justify the cover price.

Norgaard Pederson in a chapter on Maternal Alpha Feto-Protein Screening for Fetal Malformations and Down's syndrome refers to possible disadvantages including provoked miscarriage, and unnecessary anxiety in mid pregnancy, for women with false positive screening. It would have been appropriate for these questions to have been addressed by Nicolaides and colleagues in their chapter on the Role of Echocardiography in the Diagnosis of Fetal Chromosome Defects.

This is a minor criticism of a highly recommended book which should find a place in most medical libraries. The editors have made a rod for their backs of course since the rapid developments in these related fields of study will justify a second edition in the not too distant future.

R. Fraser

Book received some of which may be reviewed at a later date

Scientific Foundations of Obstetrics and Gynaecology edited by Elliot Philipp & Marcus Setchell with Jean Ginsberg. Butterworth Heinemann, Oxford, 1991, 764 pages, fully illustrated, £125

Reproductive Endocrinology, Third edition edited by Samuel S. C. Yen & Robert B. Jaffe. W. B. Saunders Co. Philadelphia, London, 1991, 1016 pages, fully illustrated, £90.00

Urogynecology and Urodynamics. Theory and Practice edited by Donald R. Ostergard & Alfred E. Bent. Williams & Wilkins, Baltimore, 1991, 610 pages, with figures, tables and photographic plates, £73.00

HIV and AIDS in Mothers and Babies A Guide to Counselling by Lorraine Sherr. Blackwell Scientific Publications, Oxford, 1991, 218 pages, £14.95

HIV Screening of Pregnant Women and Newborns edited by Leslie M. Hardy for the Committee on Prenatal and Newborn Screening for HIV Infection, Institute of Medicine, Washington, National Academy Press, Washington, 1991, 146 pages, £16.45

The Change. Women Ageing and the Menopause by Germaine Greer. Hamish Hamilton, London, 1991, 472 pages, £16.95

The Private Life of Islam. An Algerian Diary by Ian Young. Pimlico, London, 1991, second edition, 307 pages, with illustrations, £7.50

Breast-feeding: The Biological Option. second edition by G. J. Ebrahim. Macmillan Education Ltd. London and Basingstoke, 1991, 122 pages, illustrated, £9.95 (ELBS edition £1.75, ELBS countries only)

Pathologie du Col Utérin Société Française de Gynécologie XXXV^e Assises Françaises De Gynécologie held in Nice, May 1991 Rapports Généraux Hoang-Ngoc Minh et J. Blondon. Masson, Paris, 1991, 264 pages with figures and tables, F350

Le Monitoring Électronique Foetal: La Cardiotocographie, second edition by J. M. Thoulan. Masson, Paris, 1991 200 pages, fully illustrated, F250

Echographie en Pratique Obstetricale edited by B. Guerin, Y. Ardaens, B. Bailleux & D. Houze. Masson, Paris, 1991, 208 pages, illustrated, F550

AUTHOR INDEX

- Abbott, M. Correspondence 'Nuns, virgins and spinsters' Rignon-Stern and cervical cancer revisited 1315
- Abdel Gadir, A., Khatim, M. S., Mowafi, R. S., Alnaser, H. M. I., Alzaid, H. G. N. & Shaw, R. W. Polycystic ovaries: do these represent a specific endocrinopathy? 300
- Abell, K. B. See Cuckle, H. S
- Abramovich, D. R. See Pinion, S. B
- Adoni, A. & Anteby, E. The use of Hystoacryl for episiotomy repair 476
- Adu, D. See McCormack, M. J
- Agass, M. See Coulter, A.
- Ahmed, Y. See Murdoch Eaton, D. G.
- Ahmed, Y., Sullivan, M. H. F. & Elder, M. G. Increased platelet turnover in a patient with previous recurrent pre-eclampsia and failure of aspirin therapy Case report 218
- Alexander, D. A. See Pinion, S. B
- Alford, F. See Pestell, R.
- Allan, L. See Maxwell, D. J.
- Allison, M. E. M. See Fox, J. G.
- Alnaser, H. M. I. See Abdel Gadir, A
- Alzaid, H. G. N. See Abdel Gadir, A
- Amso, N. See Morris, N
- Anand, D. See Versi, E.
- Anderson, M. See Beard, R. W
- Anderson, M. See Shaker, A. G.
- Anderson, T. F., See Loft, A.
- Anderson, M. Book review. *Postreproductive Gynaecology* 341
- Andronikou, A. D. See Mitri, F. F
- Anteby, E. See Adoni, A.
- Anthony, J. See Belfort, M. A
- Anthony, J. See Pijnenborg, R.
- Aravandinos, D. See Kalandidi, A.
- Arif, M. See Ramia, S
- Arnott, R. See Pestell, R.
- Aarnoudse, J. G. See Oosterhof, H.
- Arulkumaran, S., Nicolini, U., Fisk, N. M., Tannirandorn, Y., Rosen, K. G. & Rodeck, C. H. Direct antenatal fetal electrocardiographic waveform analysis 829
- Arumugam, K. See Mahmood, T. A.
- Ashurst, H. See Crowley, P
- Ashworth, F. Book review. *Manual of Clinical Problems in Obstetrics and Gynaecology* 339
- Ashworth, F. Book review. *Zuzpan and Quilligan's Manual of Obstetrics and Gynaecology* 339
- Ashworth, F. Book review. *Obstetrics (Colour Aids)* 339
- Aune, B. See Holst, N
- Baboolal, R. See Ohlsson, A.
- Baboonian, C. See Griffiths, P. D
- Bagshawe, K. D. See Newlands, E. S
- Baird, D. T. See Thong, K. J.
- Baker, A. C. See Lamont, R. F.
- Baker, G. See Kovacs, G.
- Baker, P. N., Broughton Pipkin, F. & Symonds, E. M. Platelet angiotensin II binding sites in normotensive and hypertensive women 436
- Baker, P. & Broughton Pipkin, F. Correspondence. Fish oil and pre-eclampsia 499
- Balfour, R. P. Correspondence. Vulval reconstruction by free tissue transfer 613
- Banfield, P. J., Scott, G. & Roberts, R. M. A modified contraceptive diaphragm for relief of uretero-vaginal fistula Case report 101
- Bangah, M. See Kovacs, G.
- Bannister, J. See Johnson, N.
- Barciulli, F. See Scrimin, F.
- Barker, D. J. P. See Robinson, S. M.
- Barker, D. J. P. See Godfrey, K. M.
- Barlow, D. See Kennedy, S
- Barlow, D. H. See Rees, M. C. P
- Barns, T. Commentary. Obstetric mortality and its causes in developing countries 345
- Barron, S. L. Commentary. Audit in obstetrics 1065
- Barron, S. L. See Leggat, H. M
- Barton, S. E. See Kell, P. D
- Bassett, C. See Tasker, M
- Batchelor, A. See Johnson, N
- Batcup, G. See Wilkinson, B. S
- Bates, T. D. See Hammond, R. H.
- Baumann, R., Magos, A. L. & Turnbull, A. Prospective comparisons of videopelviscopy with laparotomy for ectopic pregnancy 765
- Beard, R. W. See Clark, D. A.
- Beard, R. W. See Paterson, C. M.
- Beard, R. W., Kennedy, R. G., Gangar, K. F., Stones, R. W., Rogers, V., Reginald, P. W. & Anderson, M. Bilateral oophorectomy and hysterectomy in the treatment of intractable pelvic pain associated with pelvic congestion 988
- Beckley, S., Gee, H. & Newton, J. R. Scar rupture in labour after previous lower uterine segment caesarean section: the role of uterine activity measurement 265
- Beeby, A. R., Dunlop, W., Heads, A. & Hunter, S. Reproducibility of ultrasonic measurement of fetal cardiac haemodynamics 807
- Beekhuis, J. R. See van Lith, J. M. M
- Beesley, J. S. See Bonney, R. C
- Beevers, D. G. See Perry, I. J.
- Begent, R. H. J. See Newlands, E. S.
- Belfort, M. A., Anthony, J. & Kirshon, B. Respiratory function in severe gestational proteinuric hypertension. the effects of rapid volume expansion and subsequent vasodilatation with verapamil 964
- Benness, C. J. See Cutner, A.
- Bennett, A. See Schofield, M. J.
- Benzi, G. See Parazzini, F.
- Bergqvist, C. See Hellberg, D.
- Bertault, D., Mandelbrot, L., Tchobroutsky, C. & Sultan, Y. Unfavourable pregnancy outcome associated with congenital protein C deficiency. Case reports 934
- Best, J. See Pestell, R
- Bewley, S. Commentary. The future obstetrician/gynaecologist 237
- Bewley, S., Cooper, D. & Campbell, S. Doppler investigation of uteroplacental blood flow resistance in the second trimester a screening study for pre-eclampsia and intra-uterine growth retardation 871
- Bhoopalani, P. S. & Watkinson, M. Babies born before arrival at hospital 57
- Bianchi, S. See Nucci, P
- Biggs, J. S. G., Harden, R. M. & Howie, P. Undergraduate obstetrics and gynaecology in the United Kingdom and the Republic of Ireland, 1989 127
- Bigrigg, A., Chui, D., Chissel, S. & Read, M. D., Short communication. Use of intramyometrial 15-methyl prostaglandin F_{2α} to control atonic postpartum haemorrhage following vaginal delivery and failure of conventional therapy 734
- Bissenden, J. G. See Holliman, R. E.
- Bisson, D. L., MacGillivray, I., Thomas, P. & Sturatt, G. M. Correspondence. Conflicting views on the measurement of blood pressure in pregnancy 842

- Blair Bell Research Society 1304, 495
- Blake, P. R. *See* Gallagher, G. J.
- *Blake, S. & MacDonald, D The prevention of the maternal manifestations of pre-eclampsia by intensive antihypertensive treatment 244
- Boccione, L. *See* Parazzini, F.
- Bonney, R. C., Higham, J. M., Watson, H., Beesley, J. S., Shaw, R. W. & Franks, S Phospholipase activity in the endometrium of women with normal menstrual blood loss and women with proven ovulatory menorrhagia 363
- Boolell, M., *et al* *See* Pestell, R.
- Bor, R. & Johnson, M. Correspondence. The clinical presentation of women with human immunodeficiency virus infection 612
- Bourdoux, P. *See* Chanoine, J. P.
- Bradlow, J. *See* Coulter, A.
- Brancato, R. *See* Nucci, P.
- Brandes, J. M. *See* Weiner, Z.
- Breed, A. S. P. M. *See* van Lath, J. M. M.
- Brinsden, P. Book review *CRC handbook of Laboratory Diagnosis and Treatment of Infertility* 746
- Broadbent, M. & Magos, A. L. Correspondence. Management of tubal infertility in the 1900s. (Commentary) 1309
- Bromham, D. R. Correspondence. Has in vitro fertilization made salpingoscopy obsolete? (Commentary) 332
- Bromham, D. R. *See* Johnson, N.
- Brønnum-Hansen, H. *See* Loft, A.
- Brosens, J. *See* Koninckx, P. R.
- Broughton Pipkin, F. *See* Baker, P.
- Broughton Pipkin, F. *See* Loudon, K. A.
- Broughton Pipkin, F. *See* Baker, P. N.
- Broughton Pipkin, F. Correspondence. Fish-oil and pre-eclampsia 737
- Brownell, J. *See* van der Heijden, P. F. M.
- Bryce, R. L., Stanley, F. J. & Garner, J. B. Randomized controlled trial of antenatal social support to prevent preterm birth 1001
- Buckler, H. *See* Kovacs, G.
- Buckley, C. H. *See* Ridley, C. M.
- Burger, H. *See* Kovacs, G.
- Burhol, P. G. *See* Holst, N.
- Burnett, R. A. *See* Kitchenner, H. C.
- Burrell, L. M., Murdoch, A. & White, M. C. Authors' reply 116
- Burroughs, A. K. *See* Hill, N. C. W.
- Busby-Earle, R. M. C. *See* Geirsson, R. T.
- Butler, B. *See* Szarewski, A.
- Butterworth, B. H., Greer, I. A., Liston, W. A., Haddad, N. G. & Johnston, T. A. Immunocytochemical localization of neutrophil elastase in term placenta decidua and myometrium in pregnancy-induced hypertension 929
- Buxton, E. J., Leusley, D. M., Shafi, M. I. & Rollason, M. Colposcopically directed punch biopsy: a potentially misleading investigation 1273
- Buller, H. R. *See* De Boer, K.
- *Cacciatori, B., Tutunen, A. & Ylostalo, P. Authors' reply 331
- Cahill, D. J. Correspondence. Obstetric Accidents: the patient's perspective 945
- Cahill, D. J. Correspondence. Pain relief in labour (Commentary) 333
- *Calder, A. A. *See* Johnston, T. A.
- *Cameron, A. D. *See* Krishnamurthy, S.
- Campbell, D. J. *See* Wathen, N. C.
- Campbell, J. M. *See* Taylor, P. V.
- *Campbell, S. *See* Bewley, S.
- *Campbell, S. *See* Thorpe-Beeston, J. G.
- *Candiani, G. B., Fedele, L., Parazzini, F. & Villa, L. Risk of recurrence after myomectomy 385
- *Canick, J. *See* Cuckle, H. S.
- Cardozo, L. Author's reply 114
- *Cardozo, L. *See* Versi, E.
- *Cardozo, L. D. *See* Cutner, A.
- Cardozo, L. D. *See* Long, M. G.
- Cardozo, L. Book review *Introduction to Clinical Gynaecological Urology* 745
- Carroll, G. Commentary. Management of retained placenta by umbilical vein injection 348
- Carter, J. Serum bile acids in normal pregnancy 540
- Carter, P. G., Grant-Harris, V. & Wilson, P. O. G. Correspondence. Reliability of colposcopy and direct punch biopsy 232
- Cartmill, R. *See* Johnson, N.
- Caspi, E. & Langer, R. Short communication. Colpo-needle suspension for the treatment of urinary stress incontinence—a new technique 1183
- Cass, P. L. *See* Wathen, N. C.
- Chalk, P. *See* Morris, N.
- Chalmers, B. E. *See* Hofmeyr, G. J.
- Chamberlain, G. & Pearce, J. M. Commentary. The flying squad 1067
- Chamberlain, G. Correspondence. Litigation in obstetrics and gynaecology. (Commentary) 1185
- Chamberlain, G., Freeman, R., Price, F., Kennedy, A., Green, D. & Eve, L. A comparative study of ethamsylate and mefenamic acid in dysfunctional uterine bleeding 707
- Chandran, R. & Redman, C. W. G. Correspondence. Postpartum eclampsia and acute renal failure; treatment with prostacyclin. Case report 1055
- Chandran, R., Serra Serra, V., Sellers, S. M. & Redman, C. W. G. Fetal middle cerebral artery velocity waveforms—a terminal pattern. Case report 937
- Chanoine, J. P., Toppet, V., Bourdoux, P., Spehl, M. & Delange, F. Smoking during pregnancy: a significant cause of neonatal thyroid enlargement 65
- Chapman, M. G. *See* Ruparelia, B. A.
- Chapple, J. C. *See* Paterson, C. M.
- Chard, T. *See* Kent, A.
- Chard, T. *See* Nasri, M. N.
- Chard, T. *See* Wathen, N. C.
- Charnock, M. *See* Frith, P.
- Chissel, S. *See* Bignig, A.
- Christiaens, G. C. M. L., Nieuwenhuis, H. K., Von Dem Borne, K. A. E. G., Ouwehand, W. H., Van Dalen, C. M., Helmerhorst, F. M. & Van Der Tweel, I. Correspondence. Authors' reply 335
- Chua, S., Wilkins, T., Sargent, I. & Redman, C. Trophoblastic deportation in pre-eclamptic pregnancy 973
- Chui, D. *See* Bigrigg, A.
- Clark, D. A. & Beard, R. W. Authors' reply 611
- Clark, L., Mugford, M. & Paterson, C. How does the mode of delivery affect the cost of maternity care? 519
- Clarke, D. G. *See* Hammond, R. H.
- Clarke, L. *See* Fox, R.
- Clayton-Smith, J. Book review. *Birth Defects Encyclopedia* 949
- Clements, R. V. Commentary. Litigation in obstetrics and gynaecology 424
- Clewlow, F. *See* Newbold, S.
- Coffer, A. *See* Fraser, D.
- Cohn, M. & Stewart, P. Pretreatment of the primigravid uterine cervix with mifepristone 30 h prior to termination of pregnancy: a double blind study 778
- Cole, T. J. *See* Coley, N. V.
- Coley, N. V., Tremble, J. M., Henson, G. L. & Cole, T. J. Head circumference/abdominal circumference ratio, ponderal index and fetal malnutrition. Should head circumference/abdominal circumference ratio be abandoned? 524
- Collins, A. *See* Murphy, K. W.
- Connelly, A. *See* Trudinger, B. J.
- Constantine, G. *See* McCormack, M. J.
- Constantine, G. *See* Holliman, R. E.
- Constantine, G., Fitzgibbon, N. & Weaver, J. B. Correspondence. anti-Kell in pregnancy 943
- Conti, E. *See* Nucci, P.
- Cook, C. M. *See* Trudinger, B. J.
- Cook, C. M. & Trudinger, B. J. Maternal angiotensin and fetal Doppler umbilical artery flow waveforms 698

- Cook, R. *See* Marteau, T. M.
 Cooke, D. *See* Singhal, V.
 Cooke, I. D. *See* Li, T. C.
 Cooper, D. *See* Versi, E.
 Cooper, D. *See* Bewley, S.
 Corrigan, E. *See* Fox, R.
 Coulson, R. *See* Mahomed, K.
 Coulter, A., Bradlow, J., Agass, M., Martin-Bates, C. & Tulloch, A. Outcomes of referrals to gynaecology outpatients clinics for menstrual problems: an audit of general practice records 789
 Crabbe, D. *See* Johnson, N.
 Creed, F. *See* Mutale, T.
 Creighton, S. M. & Stanton, S. L. The surgical management of vaginal vault prolapse 1150
 Creighton, S. M., Pearce, J. M., Robson, I., Wang, K. & Stanton, S. L. Sensory urgency: how full is your bladder? 1287
 Creighton, S. M., Plevnik, S. & Stanton, S. L. Distal urethral electrical conductance (DUEC)—a preliminary assessment of its role as a quick screening test for incontinent women 69
 Crofts, S. L. & Wilson, E. Epidural analgesia for labour in Takayasu's arthritis Case report 408
 Crook, D. & Stevenson, J. C. Commentary Progestogens, lipid metabolism and hormone replacement therapy 749
 Crowley, P., Elbourne, D., Ashurst, H., Garcia, J., Murphy, D. & Duignan, N. Delivery in an obstetric birth chair: a randomized controlled trial 667
 Cuckle, H. *See* Wald, N.
 Cuckle, H. S., Wald, N. J., Densem, J. W., Canick, J. & Abeil, K. B. Second trimester amniotic fluid oestriol, dehydroepiandrosterone sulphate, and human chorionic gonadotrophin levels in Down's syndrome 1160
 Cullen, S. *See* Turner, M. J.
 Cutner, A., Cardozo, L. D. & Benness, C. J. Assessment of urinary symptoms in early pregnancy 1283
 Cutner, A., Cardozo, L. D. & Wise, B. G. Short communication The effects of pregnancy on previous incontinence surgery Case report 1181
 Cuzick, J. *See* Szaewski, A.
 Cuzick, J. *See* Szaewski, A.
 Danielian, P. J. Short communication CA 125 and preterm prelabour rupture of the membranes 835
 Danon, Y. L. *See* Seidman, D. D.
 Dugaard, H. O. *See* Sørensen, F. B.
 Dave, K. Correspondence. External cephalic version at term: how high are the stakes? Commentary 839
 Davey, D. A. *See* Pijnenborg, R.
 Davis, J. A. Book review. *Endoscopic Laser Surgery (Clinical Practice of Gynaecology, Vol. 2)* 507
 Davis, N. *See* Garden, A.
 Davison, J. M. *See* Macphail, S.
 Dawes, J. *See* Johnston, T. A.
 Dawes, M. G. & Grudzinskas, J. G. Patterns of maternal weight gain in pregnancy 195
 Dawes, M. G. & Grudzinskas, J. G. Repeated Measurement of maternal weight during pregnancy Is this a useful practice? 189
 Dawes, M. G. & Grudzinskas, J. G. Correspondence. Authors' reply 1056
 De Boer, K., Büller, H. R., Ten Cate, J. W. & Treffers, P. E. Coagulation studies in the syndrome of haemolysis, elevated liver enzymes and low platelets 42
 De Boo, T. *See* Steegers, E. A. P.
 de Bruijn, H. W. A. *See* van Lith, J. M. M.
 de Martino, M. *See* Tovo, P. A.
 de Swiet, M. Commentary Blood pressure measurement in pregnancy 239
 Delange, F. *See* Chanoine, J. P.
 Denman, A. M. Book review *The Immunology of the Fetus* 341
 Densem, J. W. *See* Cuckle, H. S.
 Diepeveen, D. A. *See* Newnham, J. P.
 Dimitry, E. S. *See* Oskarsson, T.
 Dimitry, E. S. *See* Soussis, I.
 Djahanbakhch, O. *See* Maguiness, S. D.
 Dockery, P. *See* Li, T. C.
 Dodd, K. *See* Hull, J.
 Doesburg, W. H. *See* Poeschmann, R. P.
 Dørup, I. *See* Skajaa, K.
 Doulgerakis, M. *See* Kalandidi, A.
 Doyle, P. M. Correspondence The future obstetrician/gynaecologist. Commentary 840
 Drife, J. O. Book review. *Clinical Physiology in Obstetrics* Second Edition 1061
 Dubowitz, L. M. S. *See* Murdoch Eaton, D. G.
 Duignan, N. *See* Crowley, P.
 Duncan, I. D. Book review. *Kistner's Gynaecology. Principles and Practice* 421
 Duncan, I. D. *See* Gordon, H. K.
 Duncan, S. L. B. *See* Li, T. C.
 Dunlop, W. *See* Macphail, S.
 Dunlop, W. *See* Murdoch, A. P.
 Dunlop, W. *See* Murdoch, A. P.
 Dunlop, W. *See* Beeby, A. R.
 Dunn, J. *See* Shafi, M. I.
 Durmin, J. V. G. A. *See* Lawrence, M.
 Dwyer, N. A. & Stirrat, G. M. Short communication Early endometrial carcinoma: an incidental finding after endometrial resection. Case report 733
 Eckford, S. D. & Gingell, J. C. Ureteric obstruction in pregnancy—diagnosis and management 1137
 Edwards, R. *See* Szaewski, A.
 Ekman, G. *See* Granstrom, L.
 Elbourne, D. *See* Crowley, P.
 Elder, M. G. *See* Ahmed, Y.
 Elder, M. G. *See* Khan, H.
 Ennis, M. *See* Vincent, C. A.
 Erian, J. *See* Garry, R.
 Eriksen, G., Wohler, M., Ersbak, V., Hvidman, L., Hede-gaard, M. & Skajaa, K. Placental abruption. A case-control investigation 448
 Ersbak, V. *See* Eriksen, G.
 Eskes, T. K. A. B. *See* Poeschmann, R. P.
 Eskes, T. K. A. B. *See* Steegers, E. A. P.
 Eustace, D. L. S. *See* Hammond, R. H.
 Evans, B. E. *See* Furlonge, C. B.
 Evans, J. Fetal crown-rump length values in the first trimester based upon ovulation timing using the luteinizing hormone surge 48
 Eve, L. *See* Chamberlain, G.
 Everett, J. Book review *Health Care of Women and Children in Developing Countries* 1190
 Fagin, D. G. Book review. *Textbook of Fetal and Perinatal Pathology* 744
 Fairlie, F. *See* Krishnamurthy, S.
 Fairlie, F. *See* Whittle, M.
 Fairlie, F. M. & Walker, J. J. Correspondence. Maternal and fetal haemodynamics in hypertensive pregnancies during maternal treatment with intravenous hydralazine or labetalol 1186
 Faratian, B. *See* Shelton, K.
 Farquharson, R. G. *See* Taylor, W. G.
 Fast, J. H. *See* Steegers, E. A. P.
 Fedele, L. *See* Candiani, G. B.
 Fedele, L. *See* Parazzini, F.
 Felton, C. V. *See* Thorpe-Beeston, J. G.
 Ferguson, J. A., Goldacre, M. J., Henderson, J. & Gillmer, M. D. G. Audit of workload in gynaecology: analysis of time trends from linked statistics 772
 Fergusson, I. L. C. *See* Trehan, A. K.
 Fiander, A. Correspondence. Obstetric mortality and its causes in developing countries 841
 Finn, C. B. *See* Shafi, M. I.
 Fish, A. *See* Prys Davies, A.
 Fishel, S. *See* Shelton, K.

- Fisher, J. *See* Johnson, N.
 Fisk, N. M. *See* Arulkumaran, S.
 Fisk, N. M. *See* Nicolini, U.
 Fisk, R. A. *See* Taylor, W. G.
 Fitzgibbon, N. *See* Constantine, G.
 Flannelly, G. M. *see* Turner, M. J.
 Fong, E. *See* Trudinger, B. J.
 Fong, K. *See* Ohlsson, A.
 Forbes, C. D. *See* Greer, I. A.
 Fors, B. *See* Hellberg, D.
 Fowler, C. G. *See* Gallagher, G. J.
 Fox, J. G., Sutcliffe, N. P., Walker, J. J. & Allison, M. E. M. Postpartum eclampsia and acute renal failure: treatment with prostacyclin. Case report 400
 Fox, R., Corrigan, E., Thomas, P. G., & Hull, M. G. R. Oestrogen and androgen states in oligo-amenorrhoeic women with polycystic ovaries 294
 Fox, R. Correspondence. Autoimmune ovarian failure with elevated serum levels of luteinizing hormone and enlarged ovaries 115
 Fox, R., Wardle, P. G., Clarke, L. & Hull, M. G. R. Acromegaly bone changes in severe polycystic ovarian disease: an effect of hyperinsulinaemia? case report 410
 Fox, S. C. *See* Loudon, K. A.
 Frank, P. I., McNamee, R., Hannaford, P. C., Kay, C. R. & Hirsch, S. The effect of induced abortion on subsequent pregnancy outcome 1015
 Franks, S. *See* Bonney, R. C.
 Fraser, C. *See* Mahmood, T. A.
 Fraser, D., Padwick, M. L., Whitehead, M., Coffey, A. & King, R. J. B. Presence of an oestradiol receptor-related protein in the skin: changes during the normal menstrual cycle 1277
 Fraser, R. Book review *Adipose Tissue and Reproduction (Progress in Reproductive Biology and Medicine Vol 14)* 234
 Fraser, R. Book review *Immunobiology of Normal and Diabetic Pregnancy* 747
 Fraser, R. Book review *The Embryo: Normal and Abnormal Development and growth* 1318
 Fraser, R. Correspondence. Intrauterine pressures in labours induced by amniotomy and oxytocin or vaginal prostaglandin gel, compared with spontaneous labour 1314
 Fraser, W. Author's reply 1060
 Fraser, W. D., Sauve, R., Parboosingh, I. J., Fung, T., Sokol, R. & Presaud, D. A randomized controlled trial of early amniotomy 84
 Freeman, R. *See* Chamberlain, G.
 Freeman, R. M. Placenta accreta and myotonic dystrophy. Two case reports 594
 Fribourg, S. Correspondence. The use of Hystoacryl for episiotomy repair
 Frith, P., Charnock, M. & Wojnarowska, F. Cicatricial pemphigoid diagnosed from ocular features in recurrent severe vulval scarring. Two case reports 482
 Fung, T. *See* Fraser, W. D.
 Furlonge, C. B., Thin, R. N., Evans, B. E. & McKee, P. H. Vulvar vestibulitis syndrome: a clinico-pathological study 703
 Gabiano, C. *See* Tovo, P. -A.
 Gafar, A. *See* Giles, J. A.
 Gale, R. *See* Seidman, D. D.
 Gallagher, G. J., Oliver, R. T. D., Oram, D. H., Fowler, C. G., Blake, P. R., Mantell, B. S., Slevin, M. L. & Hope-Stone, H. F. A new treatment for endometrial cancer with gonadotrophin releasing-hormone analogue 1037
 Galli, L. *See* Tovo, P. -A.
 Gamsu, H. *See* Long, M. G.
 Gangar, K. & Whitehead, M. I. Correspondence. Hormone implants and tachyphylaxis 607
 Gangar, K. F. *See* Beard, R. W.
 Garcia, J. *See* Crowley, P.
 Garden, A., Johnston, M. & Davis, N. Short communication. Intrauterine infection and miscarriage following trans-abdominal chorionic villus sampling. Case report 413
 Garden, A. S., Weindling, A. M., Griffiths, R. D. & Martin, P. A. Fast scan magnetic resonance imaging of fetal anomalies 1217
 Gardosi, J. *See* Schram, C. M. H.
 Garner, J. B. *See* Bryce, R. L.
 Garnett, T. J. *See* Studd, J.
 Garry, R., Erian, J. & Grochmal, S. A. A multicentre collaborative study into the treatment of menorrhagia by Nd-YAG laser ablation of the endometrium 357
 Gazzard, B. *See* Kell, P. D.
 Gee, H. *See* Oháh, K. S.
 Gee, H. *See* Beckley, S.
 Geursson, R. T. & Busby-Earle, R. M. C. Short communication. Certain dates may not provide a reliable estimate of gestational age 108
 George, L. *See* Wald, N.
 Gibb, D. M. F. *See* Long, M. G.
 Gibson, J. M. *See* Leggat, H. M.
 Giles, J. A. & Gafar, A. Commentary. The treatment of CIN do we need lasers? 3
 Giles, W. B. *See* Trudinger, B. J.
 Gill, R. *See* Torode, H.
 Gillmer, M. D. G. *See* Ferguson, J. A.
 Gilmore, I. T. *See* Taylor, W. G.
 Gingell, J. C. *See* Eckford, S. D.
 Glass, M. R. *See* Rutherford, A. J.
 Glowaczower, E. *See* Ville, Y.
 Gobetz, L. *See* Guidozzi, F.
 Godfrey, K. M., Redman, C. W. G., Barker, D. J. P. & Osmond, C. The effect of maternal anaemia and iron deficiency on the ratio of fetal weight to placental weight 886
 Godschalk, A. W. H. J. *See* Steegers, E. A. P.
 Goldacre, M. J. *See* Ferguson, J. A.
 Gonen, R. *et al.* *See* Ohlsson, A.
 Goodman, J. D. S. & Sumner, D. Patient acceptability of laser and cold coagulation therapy for pre-malignant disease of the uterine cervix 1168
 Gordon, H. K. & Duncan, I. D. Effective destruction of cervical intraepithelial neoplasia (CIN) 3 at 100°C using the Semm cold coagulator: 14 years experience 14
 Gosden, C. M. *See* Neilson, J. P.
 Granstrom, L., Ekman, G. & Malmstrom, A. Insufficient remodelling of the uterine connective tissue in women with protracted labour 1212
 Grant, A. G. *See* Hammond, R. H.
 Grant, J. M. Book review. *Medical Statistics on Microcomputers* 505
 Grant-Harris, V. *See* Carter, P. G.
 Green, D. *See* Chamberlain, G.
 Greene, K. R. *See* Westgate, J.
 Greer, I. A. *See* Butterworth, B. H.
 Greer, I. A. *See* Johnston, T. A.
 Greer, I. A., Lowe, G. D. O., Walker, J. J. & Forbes, C. D. Haemorrhagic problems in obstetrics and gynaecology in patients with congenital coagulopathies 909
 Griffiths, K. *See* Torode, H.
 Griffiths, M. 'Nuns, virgins and spinsters' Rigoni-Stern and cervical cancer revisited 797
 Griffiths, M., Hillman, G. & Usherwood, M. McD. Seat belt injury in pregnancy resulting in fetal death. A need for education? Case reports 320
 Griffiths, P. D., Baboonian, C., Rutter, D. & Peckham, C. Congenital and maternal cytomegalovirus infections in a London population 135
 Griffiths, R. D. *See* Garden, A. S.
 Grochmal, S. A. *See* Garry, R.
 Grudzinski, J. G. *See* Dawes, M. G.
 Guidozzi, F. & Gobetz, L. The tap test—a rapid bedside indicator of fetal lung maturity 479
 Gyaneshwar, R. *See* Wilkinson, C.
 Haddad, N. G. *See* Meekins, J. W.
 Haddad, N. G. *See* Butterworth, B. H.
 Haddow, J. E., Knight, G. J., Kloza, E. M., Palomaki, G. E. &

- Wald, N. J. Cotinine-assisted intervention in pregnancy to reduce smoking and low birthweight delivery 859
- Haeri, A. D. *See* Pyper, R. J. D.
- Hahn, L. *See* Hjalmarsen, A. I. M.
- Haines, A. M. R. *See* Hammond, R. H.
- Hall, M. H. Book review. *Prenatal Care Reaching Mother Reaching Infants* 118
- Hamlett, J. D. *See* Malas, H. Z.
- Hammond, R. H., Bates, T. D., Clarke, D. G., Grant, A. G., Haines, A. M. R., Eustace, D. L. S. & Heyderman, E. The immunoperoxidase localization of tumour markers in ovarian cancer: the value of CEA, EMA, cytokeratin and DD9 73
- Hangaard, J. *See* Rasmussen Loft, A. G.
- Hannaford, P. C. *See* Frank, P. I.
- Hannah, M. E. *See* Mizgala, L.
- Hansen, A. *See* Skensved, H.
- Hanssen, M., Keirse, M. J. N. C., Spitz, B. & van Assche, F. A. Angiotensin II levels in hypertensive and normotensive pregnancies 155
- Harden, R. M. *See* Biggs, J. S. G.
- Hare, J. Book review *Clinical infections in Obstetrics and Gynaecology* 504
- Hare, J. Book review *Medical Negligence Case Law* 951
- Harper, A. & Murnaghan, G. Author's reply 1187
- Harper, A. & Murnaghan, G. A Maternal and fetal haemodynamics in hypertensive pregnancies during maternal treatment with intravenous hydralazine or labetalol 453
- Harris, M. *See* Murdoch, A. P.
- Harrison, R. F. Book review. *Early Pregnancy Failure (Clinical Obstetrics & Gynaecology)* 420
- Harrison, R. F., Milner, M. & Kinsella, C. Correspondence: Litigation in obstetrics and gynaecology. (Commentary) 1185
- Havenith, M. *See* van Lijnschoten, G.
- Hawkins, D. A. *See* Kell, P. D.
- Hawkins, D. F. Correspondence: I. Repeated measurement of maternal weight during pregnancy. Is this a useful practice? II. Patterns of maternal weight gain in pregnancy 1055
- Hawthorn, R. J. S., Spowart, K., Walsh, D. & McKay Hart, D. Short communication The endometrial status of women on long-term continuous combined hormone replacement therapy 939
- Hay, C. R. M. *See* Yoong, A.
- Hayes, M. C. *See* Robinson, S. M.
- Head, C. *See* Peel, K. R.
- Heads, A. *See* Beeby, A. R.
- Healy, D. *See* Kovacs, G.
- Hodegaard, M. *See* Eriksen, G.
- Hein, P. R. *See* Steegers, E. A. P.
- Hellberg, D., Fors, B. & Bergqvist, C. Renal endometriosis treated with a gonadotrophin releasing hormone agonist. Case report 406
- Helmerhorst, F. M. *See* Christaens, G. C. M. L.
- Helmig, R. *See* Khan, H.
- Henderson, J. *See* Ferguson, J. A.
- Henshaw, R. *See* Templeton, A.
- Henshaw, R. C. & Templeton, A. A Pre-operative cervical preparation before first trimester vacuum aspiration: a randomized controlled comparison between gemeprost and mifepristone (RU 486) 1025
- Henson, G. L. *See* Colley, N. V.
- Heptinstall, S. *See* Loudon, K. A.
- Herington, A. *See* Pestell, R.
- Heyderman, E. *See* Hammond, R. H.
- Heyman, Z. *See* Ohlsson, A.
- Hibbard, B. M. Book review. *A Colour Atlas of Childbirth and Obstetric Techniques* 1317
- Higham, J. M. *See* Bonney, R. C.
- Hill, N. C. W., Morris, N. H., Shaw, R. W., Mathur, S., Rolles, K. & Burroughs, A. K. Pregnancy after orthotopic liver transplantation. Case report 719
- Hillman, G. *See* Griffiths, M.
- Hilton, P. & Mayne, C. J. The Stamey endoscopic bladder neck suspension. a clinical and urodynamic investigation, including actuarial follow-up over four years 1141
- Hirsch, P. Book review. *Clinical Practice of Gynecology Vol. I No. 2, Papillomavirus Infections* 506
- Hirsch, S. *See* Frank, P. I.
- Hjalmarsen, A. I. M., Hahn, L. & Svanberg, B. Stopping smoking in pregnancy: effect of a self-help manual in controlled trial 260
- Hodge, C. *See* Pusey, J.
- Hofmeyr, G. J. Commentary. External cephalic version at term: how high are the stakes? 1
- Hofmeyr, G. J. *See* Mitri, F. F.
- Hofmeyr, G. J., Nikodem, V. C., Wolman, W. -L., Chalmers, B. E. & Kramer, T. Companionship to modify the clinical birth environment: effects on progress and perceptions of labour, and breast-feeding 756
- Holden, L. *See* Newlands, E. S.
- Holliman, R. E. Correspondence. Author's reply 1311
- Holliman, R. E., Johnson, J. D., Constantine, G., Bissenden, J. G., Nicolaides, K. & Savva, D. Difficulties in the diagnosis of congenital toxoplasmosis by cordocentesis. Case report 832
- Holst, N., Oian, P., Aune, B., Jenssen, T. G. & Burhol, P. G. Increased plasma levels of vasoactive intestinal polypeptide in pre-eclampsia 803
- Hope-Stone, H. F. *See* Gallagher, G. J.
- Hosker, G. L. Correspondence. Commentary. Detrusor instability—current management 114
- Houwert-de Jong, M. H. Correspondence. Author's reply 336
- Howard, L. C. *See* Kell, P. D.
- Howe, D. T. & Vincenti, A. C. Is large loop excision of the transformation zone (LLETZ) more accurate than colposcopically directed punch biopsy in the diagnosis of cervical intraepithelial neoplasia? 588
- Howe, P. *See* Biggs, J. S. G.
- Hsieh, C. -C. *See* Kalandidi, A.
- Hughes, J. H. *See* Siddall-Allum, J. N.
- Hughes, S. J., Short, D. J., Usherwood, M. McD. & Tebbutt, H. Management of the pregnant woman with spinal cord injuries 513
- Hull, J. & Dodd, K. Commentary. What is birth asphyxia? 953
- Hull, M. G. R. *See* Fox, R.
- Hunt, J. *See* Oskarsson, T.
- Hunt, L. *See* Mutale, T.
- Hunter, S. *See* Beeby, A. R.
- Hurley, P. *See* Maxwell, D. J.
- Hutton, J. L. *See* Moore, K. H.
- Hvidman, L. *See* Eriksen, G.
- Hyttén, F. E. Book review *Human Sex Determination. An Historical Review and Synthesis* 615
- Hyttén, F. E. Book review. *Nutrition During Pregnancy Part I Weight Gain. Part II Nutrient Supplements* 1062
- Ilbery, M., Lyons, B. & Sundaresan, V. Ovarian necrotizing vasculitis causing major intra-abdominal haemorrhage after IVF. Case report and literature review 596
- Imrie, A. H. *See* Moore, K. H.
- Ingemarsson, I. *See* Rydstrom, H.
- Ingerslev, H. J. *See* Sørensen, F. B.
- Irving, H. *See* Johnson, N.
- Jackson, P. *See* Shelton, K.
- James, D. Book review. *Nutrition and Metabolism in Pregnancy Mother and Fetus* 949
- James, D. *See* Parker, M.
- James, D. *See* Pillai, M.
- Jansen, C. A. M. *See* Schats, R.
- Jenssen, T. G. *See* Holst, N.
- Jobbings, B. *See* Johnson, N.
- Joffe, M. *See* Paterson, C. M.
- Johanson, R. *See* Pusey, J.
- Johnson, J. *See* Shelton, K.
- Johnson, J. D. *See* Holliman, R. E.
- Johnson, M. *See* Bor, R.

- Johnson, N & Bromham, D R. Effect of cervical traction with a tenaculum on the uterocervical angle 309
- Johnson, N, Batchelor, A & Lilford, R. J. Experience with tissue expansion vaginoplasty 564
- Johnson, N, Johnson, V A., Fisher, J., Jobbings, B., Bannister, J. & Lilford, R. J. Fetal monitoring with pulse oximetry 36
- Johnson, N., Lilford, R. J. & Batchelor, A. The free-flap vaginoplasty; a new surgical procedure for the treatment of vaginal agenesis 184
- Johnson, N., Lilford, R. J., Irving, H., Crabbe, D & Cartmill, R. The vanishing bowel Case report of bowel atresia following gastroschisis 214
- Johnson, P. See Murphy, K. W
- Johnson, P. See Maxwell, D. J
- Johnson, V A. See Johnson, N.
- Johnston, M. See Garden, A.
- Johnston, M. See Marteau, T. M.
- Johnston, T. A. See Butterworth, B. H
- Johnston, T. A., Greer, I. A., Dawes, J. & Calder, A. A. Short communication. Neutrophil activation in small for gestational age pregnancies 105
- Jolley, P. See McDonald, H. M.
- Jongsma, H. W. See Steegers, E. A. P.
- Jordan, J. See Woodman, C. J. B.
- Jordan, J. A. See Shafi, M. I
- Joseph, K. S. Controlling Rh haemolytic disease of the newborn in India 369
- Joslin, C. A. F. See Peel, K. R
- Kabukoba, J. J. Correspondence: Hormone implants and tachyphylaxis 501
- Kalandidi, A., Doulgerakis, M., Tzonou, A., Hsieh, C. -C., Aravandinos, D. & Trichopoulos, D. Induced abortions, contraceptive practice, and tobacco smoking as risk factors for ectopic pregnancy in Athens, Greece 207
- Kaler, S. See Siddall-Allum, J. N
- Kay, C. R. See Frank, P. I.
- Keates, G., Peel, K. R
- Keirse, M. J. N. C. See Hanssen, M.
- Kell, P. D., Barton, S. E., Smith, D. E., Nelson, M., Marwood, R. P. & Gazzard, B. A maternal death caused by AIDS Case report 725
- Kell, P. D., Barton, S. E., Hawkins, D. A., Marwood, R. & Howard, L. C. Short communication. The clinical presentation of women with human immunodeficiency virus infection 103
- Kelly, J. See McCormack, M. J.
- Kempley, S. See Long, M. G
- Kennedy, A. See Chamberlain, G.
- Kennedy, R. G. See Beard, R. W
- Kennedy, S., Mojiminiyi, S., Soper, N., Spencer, J., Shepstone, B. & Barlow, D. Imaging of pulmonary endometriosis by immunoscintigraphy. Case report 600
- Kent, A., Kitau, M. J. & Chard, T. Short communication. Absence of diurnal variation in urinary chorionic gonadotrophin excretion at 18-13 weeks gestation 1180
- Khan, H., Sullivan, M. H. F., Helmig, R., Roseblade, C. K., Uldbjerg, N. & Elder, M. G. Quantitative production of prostaglandin E₂ and its metabolites by human fetal membranes 712
- Khatim, M. S. See Abdel Gadir, A.
- Khong, T. Y. Commentary The Robertson-Brosens-Dixon hypothesis: evidence for the role of haemochorial placental in pregnancy success 1195
- Khouri, G. G. See Peel, K. R
- Kidd, J. See Marteau, T. M.
- Kiely, J. L. Mode of delivery and neonatal death in 17 587 infants presenting by the breech 898
- Kilpatrick, D. C. Correspondence. Pre-eclampsia and antiphospholipid antibody 1313
- Kilpatrick, D. C. See Liston, W. A.
- King, P. A., Lopes, A., Tang, M. H. Y., Lam, S. K. & Ma, H. K. Theca-lutein ovarian cysts associated with placental chorioangioma. Case report 322
- King, R. J. B. See Fraser, D.
- Kinsella, C. See Harrison, R. F
- Kurshon, B. See Belfort, M. A
- Kitau, M. J. See Kent, A
- Kitau, M. J. See Wathen, N. C
- Kitchen, V. S. See Smith, J. R
- Kitchener, H. C. Book review. *Textbook of Gynecological Oncology* 1317
- Kitchener, H. C. United Kingdom Colposcopy Survey, British Society for Colposcopy and Cervical Pathology 1112
- Kitchener, H. C. See Pinion, S. B.
- Kitchener, H. C. See Shaker, A. G
- Kitchener, H. C., Neilson, L., Burnett, R. A., Young, L. & Macnab, J. C. M. Prospective serial study of viral change in the cervix and correlation with human papillomavirus genome status 1042
- Kitzinger, S. Book review. *Psychological Processes of Child-bearing* 748
- Kleijnen, J., ter Riet, G. & Knipschild, P. Authors' reply 329
- Klontzeris, L. See Li, T. C.
- Kloza, E. M. See Haddow, J. E
- Knight, G. J. See Haddow, J. E.
- Knipschild, P. See Kleijnen, J.
- Knott, P. See Maxwell, D. J
- Knox, E. G. See MacArthur, C.
- Kocjan, G. See Rubin, A
- Koninckx, P. R., Witters, K., Brosens, J., Stemers, N., Oosterlynck, D. & Meuleman, C. Conservative laparoscopic treatment of ectopic pregnancies using the CO₂-laser 1254
- Kovacs, G., Buckler, H., Bangah, M., Outch, K., Burger, H., Healy, D., Baker, G. & Phillips, S. Treatment of an ovulation due to polycystic ovarian syndrome by laparoscopic ovarian electrocautery 30
- Kramer, T. See Hofmeyr, G. J
- Kremer, J. A. M. See van der Heyden, P. F. M.
- Krishnamurthy, S., Fairlie, F., Cameron, A. D., Fairlie, F., Walker, J. J. & Mackenzie, J. R. The role of postnatal x-ray pelvimetry after caesarean section in the management of subsequent delivery 716
- Kristiansen, J. D. See Sørensen, F. B.
- Kurki, T., Laatikainen, T., Salmunen-Lappalainen, K., Laatikainen, T. & Ylikorkala, O. Maternal plasma corticotrophin-releasing hormone—elevated in preterm labour but unaffected by indomethacin or nylidrin 685
- La Vecchia, C. See Parazzini, F
- Laatikainen, T. See Kurki, T.
- Lam, S. K. See King, P. A
- Lambert, H. Book review. *Chemotherapy of Gynaecologic Cancer* 419
- Lambert, H. Book Review. *Ovarian Cancer: Biological and Therapeutic Challenges* 418
- Lamont, R. F. Correspondence. Author's reply 1315
- Lamont, R. F., Neave, S., Baker, A. C. & Steer, P. J. Intra-uterine pressures in labours induced by amniotomy and oxytocin or vaginal prostaglandin gel compared with spontaneous labour 441
- Langer, R. See Caspi, E.
- Lao, T. T. See Mizgala, L
- Laor, A. See Seidman, D. D.
- Lawrence, M., McKillop, F. M. & Durnin, J. V. G. A. Women who gain more fat during pregnancy may not have bigger babies: implications for recommended weight gain during pregnancy 254
- Lee, A. See Spencer, J. A. D
- Leggat, H. M. & Reid, M. M. Author's reply 944
- Leggat, H. M., Gibson, J. M., Barron, S. L. & Reid, M. M. Anti-Kell in pregnancy 162
- Lenton, E. A. See Li, T. C.
- Leruez, M. See Ville, Y
- Letsky, E. Book review. *Perinatology Hematology (Methods in Hematology)* 504

- Letsky, E. A. *See* Vaughan, J. I.
- Leung, A., Neale, E. & Rogers, M. Short communication. Transient improvement of umbilical arterial waveform after steroid administration 492
- Luesley, D. M. *See* Buxton, E. J.
- Lewis, M. *See* MacArthur, C
- Li, T. C. *See* Singhal, V.
- Li, T. C., Dockery, P., Ramsewak, S. S., Klentzeas, L., Lenton, E. A. & Cooke, I. D. The variation of endometrial response to a standard hormone replacement therapy in women with premature ovarian failure. An ultrasonographic and histological study 656
- Li, T. C., MacLeod, I., Singhal, V. & Duncan, S. L. B. The obstetric and neonatal outcome of pregnancy in women with a previous history of infertility: a prospective study 1087
- Lightman, S. Book review *The Climacteric Hot Flash* 1189
- Lilford, R. J. *See* Johnson, N
- Liston, W. A. & Kilpatrick, D. C. Is genetic susceptibility to pre-eclampsia conferred by homozygosity for the same single recessive gene in mother and fetus? 1079
- Liston, W. A. *See* Butterworth, B. H
- Loft, A., Anderson, T. F., Brønnum-Hansen, H., Roepstorff, C. & Madsen, M. Early postoperative mortality following hysterectomy: A Danish population based study, 1977–1981 147
- Long, M. G., Gibb, D. M. F., Kempley, S., Cardozo, L. D., Nicolaides, K. & Gamsu, H. Retention of the second twin: a viable option? Case reports 1295
- Lopes, A. *See* King, P. A.
- Louden, I. Some historical aspects of toxæmia of pregnancy. A review 853
- Louden, K. A. & Broughton Pipkin, F. Correspondence. Prediction of pregnancy-induced hypertensive disorders by angiotensin II sensitivity and supine pressor test 231
- Louden, K. A., Broughton Pipkin, F., Heptinstall, S., Fox, S. C., Mitchell, J. R. A. & Symonds, E. M. Platelet reactivity and serum thromboxane B_2 production in whole blood in gestational hypertension and pre-eclampsia 1239
- Lowe, D. G. *See* Nasri, M. N
- Lowe, G. D. O. *See* Greer, I. A.
- Lower, A. M., Mulcahy, M. T. & Yovich, J. L. Chromosome abnormalities detected in chorionic villus biopsies of failing pregnancies in a subfertile population 1228
- Luesley, D. *See* Woodman, C. J. B.
- Luesley, D. M. *See* Shafi, M. I
- Lumley, J. Commentary. Stopping smoking—again 847
- Lyons, B. *See* Ilbery, M
- Ma, H. K. *See* King, P. A.
- MacArthur, C., Lewis, M. & Knox, E. G. Commentary. Health after childbirth 1193
- MacDonald, D. *See* Blake, S
- MacDougall, J. & Siddle, N. Emergency cervical cerclage 1234
- MacGilhray, I. *See* Bisson, D. L
- Macgregor, J. E. Commentary. What constitutes an adequate cervical smear? 6
- MacKenzie, I. Book review. *A Practical Guide to Chorion Villus Sampling* 1318
- Mackenzie, I. Z. Book review *Human Prenatal Diagnosis* 950
- Mackenzie, J. R. *See* Krishnamurthy, S
- MacLeod, I. *See* Li, T. C.
- MacLeod, K. G. A. Book review *Anaesthetic and Obstetric Management of High-Risk Pregnancy* 1189
- Macnab, J. C. M. *See* Kitchener, H. C
- Macphail, S., Thomas, T. H., Wilkinson, R., Dunlop, W. & Davison, J. M. Erythrocyte hydration in normal human pregnancy 1205
- Madsen, M. *See* Loft, A
- Magos, A. Book review. *Baillière's Clinical Obstetrics and Gynaecology International Practice and Research, Vol. 3, No. 3, September 1989* 614
- Magos, A. L. *See* Broadbent, M.
- Magos, A. L. *See* Baumann, R.
- Maguiness, S. D. & Djahanbakhch, O. Short communication. Tuboscopy in a previously sterilized patient 326
- Maguire, R. *See* Turner, M. J
- Mahmood, T. A. & Templeton, A. Prenatal fluid volume and sex steroids in the pre-ovulatory period in mild endometriosis 179
- Mahmood, T. A., Arumugam, K. & Templeton, A. A. Oocyte and follicular fluid characteristics in women with mild endometriosis 573
- Mahmood, T. A., Messinis, I. E. & Templeton, A. Follicular development in spontaneous and stimulated cycles in women with minimal-mild endometriosis 783
- Mahmood, T. A., Templeton, A. A., Thomas, L. & Fraser, C. Menstrual symptoms in women with pelvic endometriosis 558
- Mahomed, K., Seeras, R. & Coulson, R. External cephalic version at term. A randomized controlled trial using tocolysis 8
- Mahroo, M. *See* Murdoch, A. P.
- Malas, H. Z. & Hamlett, J. D. Acute recurrent polyhydramnios—management with indomethacin 583
- Malmstrom, A. *See* Granstrom, L
- Maloney, M. D. *See* Taylor, P. V.
- Mandelbröt, L. *See* Bertault, D
- Mann, J. *See* Thorogood, M
- Mantell, B. S. *See* Gallagher, G. J.
- Mantingh, A. *See* van Lith, J. M. M
- Manyonda, I. T. & Pearce, J. M. Correspondence. A morphological and immunological study of human placental bed biopsies in miscarriage 609
- Marchant, S. Book review *Midwifery Practice Postnatal Care. A Research-Based Approach* 844
- Marcussen, N. *See* Sørensen, F. B.
- Mareh, M. *See* Mutale, T.
- Margara, R. *See* Soussis, I.
- Margara, R. A. *See* Winston, R. M. L
- Marteau, T. M., Kidd, J., Cook, R., Michie, S., Johnston, M., Slack, J. & Shaw, R. W. Perceived risk not actual risk predicts uptake of amniocentesis 282
- Martin, P. A. *See* Garden, A. S.
- Martin, T. *See* Vincent, C. A.
- Martin-Bates, C. *See* Coulter, A.
- Marwood, R. P. *See* Kell, P. D
- Mashiach, S. *See* Seidman, D. D.
- Mathur, S. *See* Hill, N. C. W
- Maxwell, D. J., Johnson, P., Hurley, P., Neales, K., Allan, L. & Knott, P. Fetal blood sampling and pregnancy loss in relation to indication 892
- Maxwell, R. *See* Srivastava, S
- Mayne, C. J. *See* Hilton, P.
- McCormack, M. J., Adu, D., Weaver, J., Michael, J. & Kelly, J. Anti-platelet antibodies, a prognostic marker in pregnancies associated with lupus nephritis. Case report 324
- McCormack, M. J. & Constantine, G. Correspondence: Fish-oil and pre-eclampsia 738
- McCusker, C. *See* Wilkinson, C
- McDonald, H. M., O'Loughlin, J. A., Jolley, P., Vigneswaran, R. & McDonald, P. J. Vaginal infection and preterm labour 427
- McDonald, P. J. *See* McDonald, H. M
- McFaul, P. Book review. *Gift From Basic to Clinics* 118
- McGarry, J. Book review *The No Hysterectomy Option. Your Body—Your Choice* 845
- McGarry, J. Book Review. *Physiotherapy in Obstetrics & Gynaecology* 745
- McKay Hart, D. *See* Hawthorn, R. J. S.
- McKee, P. H. *See* Furlonge, C. B.
- McKelvie, P. *See* Pestell, R.
- McKillop, F. M. *See* Lawrence, M
- McNamee, R. *See* Frank, P. I.
- Meekins, J. W. & Haddad, N. G. Correspondence. Use of Gynoecheck endometrial tissue sampler in infertility 115
- Messinis, I. E. *See* Mahmood, T. A.
- Meuleman, C. *See* Koninckx, P. R

- Mezzanotte, G. See Parazzini, F.
 Mgaya, H. See Peel, K. R.
 Michael, J. See McCormack, M. J.
 Michue, S. See Marteau, T. M.
 Mikhail, M. See Nathan, B.
 Miller, I. D. See Shaker, A. G.
 Mills, M. S. Correspondence. The crown-rump length in early human pregnancy: a reappraisal 946
 Mills, M. S. See Oskarsson, T.
 Milner, M. See Harrison, R. F.
 Mitchell, J. R. A. See Loudon, K. A.
 Mitri, F. F., Andronikou, A. D., Perpinyal, S., Hofmeyr, G. J. & Sonnendecker, E. W. W. A clinical comparison of sonographic hydrotubation and hysterosalpingography 1031
 Mizgala, L., Lao, T. T. & Hannah, M. E. Hypothyroidism presenting as hypothermia following pre-eclampsia at 23 weeks gestation. Case report and review of the literature 221
 Mojumiyi, S. See Kennedy, S.
 Möller, J. See Sørensen, F. B.
 Monaghan, J. M. See Nwabineh, N. J.
 Moore, K. H., Richmond, D. H., Sutherst, J. R., Imrie, A. H. & Hutton, J. L. Crouching over the toilet seat: prevalence among British gynaecological outpatients and its effect upon micturition 569
 Morris, J. E. Book review. *A Clinical Guide for the Care of Older Women* 119
 Morris, N., Amsio, N. & Chalk, P. Haematometra secondary to hormone replacement therapy. Case report 837
 Morris, N. H. See Hill, N. C. W.
 Mortensen, V. See Rasmussen Loft, A. G.
 Mowafi, R. S. See Abdel Gadir, A.
 Mugford, M. Book review. *Baillière's Clinical Obstetrics and Gynaecology. International Practice and Research. Vol. 4. No. 1. Antenatal Care, March 1990* 337
 Mugford, M. See Clark, L.
 Mulcahy, M. T. See Lower, A. M.
 Munday, P. E. Book review. *Sexually Transmitted Disease. A Textbook of Genitourinary Medicine* 1190
 Murdoch Eaton, D. G., Ahmed, Y. & Dubowitz, L. M. S. Maternal trauma and cerebral lesions in preterm infants. Case report 1292
 Murdoch, A. See Burrell, L. M.
 Murdoch, A. P., Harris, M., Mahroo, M., Williams, M. & Dunlop, W. Gamete intrafallopian transfer (GIFT) compared with intrauterine insemination in the treatment of unexplained infertility 1107
 Murdoch, A. P., Harris, M., Mahroo, M., Williams, M. & Dunlop, W. Is GIFT (gamete intrafallopian transfer) the best treatment for unexplained infertility? 643
 Murnaghan, G. See Harper, A.
 Murnaghan, G. A. See Harper, A.
 Murphy, D. See Crowley, P.
 Murphy, K. W., Russell, V., Collins, A. & Johnson, P. The prevalence, aetiology and clinical significance of pseudo-sinusoidal fetal heart rate patterns in labour 1093
 Murphy, M. See Thorogood, M.
 Murray, K. See Tasker, M.
 Mutale, T., Creed, F., Maresh, M. & Hunt, L. Life events and low birthweight—analysis by infants preterm and small for gestational age 166
 Nasrat, H. See Nicolini, U.
 Nasri, M. N., Shepherd, J. H., Setchell, M. E., Lowe, D. G. & Chard, T. The role of vaginal scan in measurement of endometrial thickness in menopausal women 470
 Nasri, M. N., Shepherd, J. H., Setchell, M. E., Lowe, D. G. & Chard, T. Transvaginal ultrasound. A reliable basis for clinical management? Case reports 485
 Nathan, B. & Mikhail, M. Short communication. Avicenna's recipe for contraception 1303
 Neale, E. See Leung, A.
 Neales, K. See Maxwell, D. J.
 Neave, S. See Lamont, R. F.
 Neilson, J. Book review. *Handbook of Ultrasound and Gynecology Volumes I & II* 1063
 Neilson, J. P. & Gosden, C. M. First trimester prenatal diagnosis. chorion villus sampling or amniocentesis? 849
 Neilson, L. See Kitchener, H. C.
 Nelson, M. See Kell, P. D.
 Newbold, S., Wheeler, T. & Clewlow, F. Correspondence. Authors' reply 1058
 Newbold, S., Wheeler, T. & Clewlow, F. Comparison of the T/QRS ratio of the fetal electrocardiogram and the fetal heart rate during labour and the relation of these variables to condition at delivery 173
 Newlands, E. S., Bagshawe, K. D., Begent, R. H. J., Rustin, G. J. S. & Holden, L. Results with the EMA/CO (etoposide, methotrexate, actinomycin D, cyclophosphamide, vincristine) regimen in high risk gestational trophoblastic tumours, 1979 to 1989 550
 Newnham, J. P., O'Dea, M. R. -A., Reid, K. P. & Diepeveen, D. A. Dopplerflow velocity waveform analysis in high risk pregnancies—a randomized controlled trial 956
 Newton, J. R. See Beckley, S.
 Ng, S. See Trudinger, B. J.
 Nicolaides, K. See Long, M. G.
 Nicolaides, K. See Holliman, R. E.
 Nicolaides, K. H. See Thorpe-Beeston, J. G.
 Nicolaides, K. H. See Ribbert, L. S. M.
 Nicolaïdis, P. See Spencer, J. A. D.
 Nicolaïdis, P. See Nicolini, U.
 Nicolini, U. See Arulkumaran, S.
 Nicolini, U. See Spencer, J. A. D.
 Nicolini, U., Nicolaïdis, P., Tannirandorn, Y., Fisk, N. M., Nasrat, H. & Rodeck, C. H. Fetal liver dysfunction in Rh alloimmunization 287
 Niewenhuys, H. K. See Christiaens, G. C. M. L.
 Nikodem, V. C. See Hofmeyr, G. J.
 Nip, M. M. C. See Taylor, P. V.
 Nørgaard-Pedersen, B. See Rasmussen Loft, A. G.
 Norman, S. G. An audit of the management of ectopic pregnancy 1267
 Nucci, P., Conti, E., Bianchi, S., Pierro, L. & Brancato, R. Short communication. Diplopia after labour. Case report 227
 Nwabineh, N. J. & Monaghan, J. M. Vaginal epithelial abnormalities in patients with CIN: clinical and pathological features and management 25
 O'Dea, M. R. -A. See Newnham, J. P.
 O'Donovan, P. J. See Peel, K. R.
 O'Loughlin, J. A. See McDonald, H. M.
 Oakley, A. Book review. *Miscarriage Women's Experience and Needs* 949
 Oates, S. Correspondence. Patient selection for hysteroscopic endometrial resection 948
 Ohlsson, A., Fong, K., Hannah, M., Heyman, Z., Gonen, R., Rose, T. & Baboolal, R. Prediction of lethal pulmonary hypoplasia and chorioamnionitis by assessment of fetal breathing 692
 Øian, P. See Holst, N.
 Okuda, K. J. See Thomas, E. J.
 Oliver, R. T. D. See Gallagher, G. J.
 Olsen, S. F. See Secher, N. J.
 Oláh, K. S. & Gee, H. Fetal heart block associated with maternal anti-Ro (SS-A) antibody—current management. A review 751
 Oláh, K. S. & Redman, C. W. G. Overlap syndrome and its implications in pregnancy. Case report 728
 Oláh, K. S. J. & Gee, H. Short communication. Epidural analgesia—a cause of transient impairment of the utero-placental circulation? 1174
 Oosterhof, H. & Aarnoudse, J. G. Placental abruption preceded by abnormal flow velocity waveforms in the uterine arteries. Case report 225
 Oosterlynck, D. See Koninckx, P. R.
 Oram, D. H. See Gallagher, G. J.

- Oram, D. See Prys Davies, A.
 Oskarsson, T. See Soussis, I.
 Oskarsson, T., Dimitry, E. S., Mills, M. S., Hunt, J. & Winston, R. M. L. Attitudes towards gamete donation among couples undergoing in vitro fertilization 351
 Osmond, C. See Godfrey, K. M.
 Osmond, C. See Robinson, S. M.
 Ouwehand, W. H., See Christiaens, G. C. M. L.
 Outch, K. See Kovacs, G.
 Owen, P. Correspondence. Ideopathic thrombocytopenic purpura in pregnancy. A randomized trial on the effect of antenatal low dose corticosteroids on neonatal platelet count 948
 Padwick, M. L. See Fraser, D.
 Palomaki, G. E. See Haddow, J. E.
 Palomba, E. See Tovo, P. -A.
 Parazzini, F. See Candiani, G. B.
 Parazzini, F., Tozzi, L., Mezzanotte, G., Bocciolone, L., La Vecchia, C., Fedele, L. & Benzi, G. Trends in multiple births in Italy. 1955-1983 535
 Parboosingh, I. J. See Fraser, W. D.
 Parker, M. & James, D. Spontaneous variation in fetal pleural effusions. Case report 403
 Parkin, D. E. See Pinion, S. B.
 Parmar, R. See Taylor, P. V.
 Parry, V. Book review. *The Baby Machine. Reproductive Technology and the Commercialization of Motherhood* 614
 Paterson, C. See Clark, L.
 Paterson, C. M., Chapple, J. C., Beard, R. W., Jo'ffe, M., Steer, P. J. & Wright, C. S. W. Evaluating the quality of the maternity services—a discussion paper 1073
 Pearce, J. M. See Chamberlain, G.
 Pearce, J. M. See Creighton, S. M.
 Pearce, J. M. See Manyonda, I. T.
 Peckham, C. See Griffiths, P. D.
 Pedersen, J. F., Sørensen, S. & Ruge, S. Short communication. Serum level of secretory endometrial protein PP-14 in intact ectopic pregnancy 414
 Peel, K. R., Khoury, G. G., Joslin, C. A. F., O'Donovan, P. J., Mgaya, H., Keates, G., Head, C. & Thorogood, D. J. Cancer of the cervix in women under 40 years of age, a regional survey, 1975-1984 993
 Penn, Z. J. & Steer, P. J. How obstetricians manage the problem of preterm delivery with special reference to the preterm breech 531
 Perks, N. F., Sherriff, E. A. & Winston, R. M. L. Correspondence. Normal early pregnancy serum hCG levels and vaginal ultrasonography findings 330
 Perpnyal, S. See Mitri, F. F.
 Perry, I. J., Wilkinson, L. S., Shinton, R. A. & Beevers, D. G. Conflicting views on the measurement of blood pressure in pregnancy 241
 Pestell, R., Herington, A., Best, J., Boollell, M., McKelvie, P., Arnott, R. & Alford, F. Growth hormone excess and galactorrhoea without acromegalic features. Case reports 92
 Peters F., Schulze-Tollert, J. & Schuth, W. Thyrotrophin-releasing hormone—a lactation-promoting agent? 880
 Phillips, S. See Kovacs, G.
 Pierro, L. See Nucci, P.
 Pijnenborg, R., Anthony, J., Davey, D. A., Rees, A., Tiltman, A., Vercruyse, L. & Van Assche, A. Placental bed spiral arteries in the hypertensive disorders of pregnancy 648
 Pillai, M. & James, D. Continuation of normal neurobehavioural development in fetuses with absent umbilical arterial end diastolic velocities 277
 Pinton, S. B., Kitchener, H. C., Parkin, D. E., Atramovich, D. R., Russell, I. & Alexander, D. A. Correspondence. Patient selection for hysteroscopic endometrial resection 839
 Pitroff, R. & Shahib, G. Correspondence. Difficulties in the diagnosis of congenital toxoplasma by cordocentesis 1311
 Pittrof, R. Correspondence. The effects of hospitalization for rest on fetal growth, neonatal morbidity and length of gestation in twin pregnancy 416
 Plevnik, S. See Creighton, S. M.
 Poeschmann, R. P., Doesburg, W. H. & Eskes, T. K. A. B. A randomized comparison of oxytocin, sulprostone and placebo in the management of the third stage of labour 521
 Porter, R. Book review. *Female Urinary Incontinence (Proceedings of an Education Course held at the Royal College of Obstetricians and Gynaecologists, June 1989)* 341
 Presaud, D. See Fraser, W. D.
 Price, F. See Chamberlain, G.
 Prys Davies, A., Fish, A., Woolas, R. & Oram, D. Raised serum CA 125 preceding the diagnosis of carcinoma of the fallopian tube: two case reports 602
 Pugh, C. See Sheil, O.
 Purdie, D. W. Commentary. Medical education 121
 Pusey, J., Hodge, C., Wilkinson, P. & Johanson, R. Short communication. Maternal impressions of forceps or the Silcup 487
 Pyper, R. J. D. & Haeri, A. D. A review of 80 endometrial resections for menorrhagia 1049
 Ramia, S. & Arif, M. Perinatal transmission of hepatitis B virus infection. a recommended strategy for prevention and control. A review 141
 Ramsewak, S. S. See Li, T. C.
 Rasmussen Loft, A. G., Mortensen, V., Hangaard, J. & Nørgaard-Pedersen, B. Ratio of immunochemically determined amniotic fluid acetylcholinesterase to butyrylcholinesterase in the differential diagnosis of fetal abnormalities 52
 Rasmussen, M. J. See Turner, M. J.
 Read, M. D. See Bigngg, A.
 Reader, F. Book review. *The F.I.G.O. Manual of Human Reproduction. Volume 1 Reproduction Physiology. Volume 2. Family Planning. Volume 3 Reproductive Health Global Issues* 340
 Redman, C. See Chua, S.
 Redman, C. W. G. See Chandran, R.
 Redman, C. W. G. See Oláh, K. S.
 Redman, S. See Schofield, M. J.
 Redman, C. W. G. See Taylor, P. V.
 Redman, C. W. G. See Godfrey, K. M.
 Redman, C. W. G. See Sheil, O.
 Redman, C. W. G. See Chandran, R.
 Rees, A. See Pijnenborg, R.
 Rees, M. Book review. *Uterine Function. Molecular and Cellular Aspects* 1063
 Rees, M. C. P. & Barlow, D. H. Short communication. Quantitation of hormone replacement induced withdrawal bleeds 106
 Rees, M. C. P. Short communication. Role of menstrual blood loss measurements in management of complaints of excessive menstrual bleeding 327
 Reginald, P. W. See Beard, R. W.
 Reginald, P. W. See Siddall-Allum, J. N.
 Reid, K. P. See Newnham, J. P.
 Reid, M. M. See Leggat, H. M.
 Reiss, H. E. Correspondence. Author's reply 1310
 Reiss, H. Commentary. Management of tubal infertility in the 1990s 619
 Reiss, H. R. Book review. *Infertility Surgery. A Multimethod Approach to Female Reproductive Surgery* 234
 Reynolds, F. Book review. *Drugs in Pregnancy and Lactation Third Edition* 337
 Reynolds, F. Author's reply 334
 Ribbert, L. S. M., Snijders, R. J. M., Nicolaidis, K. H. & Visser, G. H. A. Relation of fetal blood gases and data from computer-assisted analysis of fetal heart rate patterns in small for gestation fetuses 820
 Richmond, D. Book review. *Micturition* 845
 Richmond, D. H. See Moore, K. H.
 Ridley, C. M. & Buckley, C. H. Correspondence. Darier's disease localized to the vulva 112

- Roberts, L. J. & Young, K. R. The management of prolonged pregnancy—an analysis of women's attitudes before and after term 1102
- Roberts, L. J. Commentary Elective section after two sections—where's the evidence? 1199
- Roberts, L. J. Correspondence Ideopathic thrombocytopenic purpura in pregnancy: A randomized trial on the effect of antenatal low dose corticosteroids on neonatal platelet count 334
- Roberts, R. M. See Banfield, P. J.
- Robertson, J. N. See Ville, Y.
- Robinson, S. M., Wheeler, T., Hayes, M. C., Barker, D. J. P. & Osmond, C. Fetal heart rate and intrauterine growth 1223
- Robson, I. See Creighton, S. M.
- Rodeck, C. H. See Arulkumaran, S.
- Rodeck, C. H. See Nicolini, U.
- Rodeck, C. H. See Spencer, J. A. D.
- Roeperstorff, C. See Loft, A.
- Rogers, M. See Leung, A.
- Rogers, V. See Beard, R. W.
- Rolland, R. See van der Heijden, P. F. M.
- Rollason, M. See Buxton, E. J.
- Rollason, T. P. Book review. *Female Reproductive System (Systemic Pathology, Third Edition, Vol. 6)* 1061
- Rolles, K. See Hill, N. C. W.
- Ronen, N. See Weiner, Z.
- Rose, Y. See Ohlsson, A.
- Roseblade, C. K. See Khan, H.
- Rosen, K. G. See Arulkumaran, S.
- Rubin, A. & Kocjan, G. Correspondence. The use of cervicography in a primary screening service 740
- Ruge, S. See Pedersen, J. F.
- Rugman, F. P. See Yoong, A.
- Ruparelia, B. A. & Chapman, M. G. Correspondence Early identification of placenta praevia 499
- Rushton, D. I. West Midlands perinatal mortality survey, 1987. An audit of 300 perinatal autopsies 624
- Russell, I. See Pinon, S. B.
- Russell, V. See Murphy, K. W.
- Rustin, G. J. S. See Newlands, E. S.
- Rutherford, A. J., Glass, M. R., & Wells, M. Short communication. Patient selection for hysteroscopic endometrial resection 228
- Rutter, D. See Griffiths, P. D.
- Ryan, R. See Turner, M. J.
- Ryan, G. See Whittle, M.
- Rydhstrom, H. & Ingemarsson, I. A case-control study of the effects of birth by caesarean section on intrapartum and neonatal mortality among twins weighing 1500–2499 g 249
- Salmunen-Lappalainen, K. See Kurki, T.
- Sandstrom, B. -M. See Skajaa, K.
- Sansom-Fisher, R. W. See Schofield, M. J.
- Sargent, I. See Chua, S.
- Sauve, R. See Fraser, W. D.
- Savva, D. See Holliman, R. E.
- Savvas, M. Book review. *The Greek Way of Life* 117
- Schats, R., Van Os, H. C., Jansen, C. A. M. & Wladimiroff, J. W. The crown-rump length in early human pregnancy: a reappraisal 460
- Schofield, M. J., Bennett, A., Redman, S., Walters, W. A. W. & Sansom-Fisher, R. W. Self-reported long-term outcomes of hysterectomy 1129
- Schram, C. M. H. & Gardosi, J. Correspondence. The effect of caput succedaneum on oxygen saturation measurements 113
- Schulze-Tollert, J. See Peters, F.
- Schuth, W. See Peters, F.
- Scott, G. See Banfield, P. J.
- Scrimin, F., Volpe, C., Tracanzan, G., Toffoletti, F. G. & Barciulli, F. Vulvodynia and selective IgA deficiency. Case reports 592
- Secher, N. J., Olsen, S. F. & Sorensen, J. D. Authors' reply 739
- Seeras, R. See Mahomed, K.
- Seidman, D. D., Laor, A., Gale, R., Stevenson, D. K., Mashlach, S. & Danon, Y. L. Pre-eclampsia and offspring's blood pressure, cognitive ability and physical development at 17 years of age 1009
- Selinger, M. Commentary. Immunoprophylaxis for rhesus disease—expensive but worth it? 509
- Sellers, S. M. See Chandran, R.
- Serra Serra, V. See Chandran, R.
- Setchell, M. E. See Nasri, M. N.
- Shafi, M. I. See Buxton, E. J.
- Shafi, M. I., Finn, C. B., Luesley, D. M., Jordan, J. A. & Dunn, J. Short communication. Lesion size and histology of atypical cervical transformation zone 490
- Shahib, G. See Pitroff, R.
- Shaker, A. G., Anderson, M., Kitchener, H. C. & Miller, I. D. Short communication. An out-patient approach to the management of postmenopausal bleeding 488
- Shaw, R. W. See Abdel Gadir, A.
- Shaw, R. W. See Marteau, T. M.
- Shaw, R. W. See Bonney, R. C.
- Shaw, R. W. See Hill, N. C. W.
- Sheil, O., Redman, C. W. G. & Pugh, C. Renal failure in pregnancy due to primary renal lymphoma. Case report 216
- Shelton, K., Fishel, S., Jackson, P., Webster, J., Faratian, B. & Johnson, J. The use of the GnRH analogue buserelin for IVF—does it improve fertility? 544
- Shepherd, J. H. See Nasri, M. N.
- Shepstone, B. See Kennedy, S.
- Sherriff, E. A. See Perks, N. F.
- Sheth, S. S. The place of oophorectomy at vaginal hysterectomy 662
- Shinton, R. A. See Perry, I. J.
- Short, D. J. See Hughes, S. J.
- Siddall-Allum, J. N., Hughes, J. H., Kaler, S. & Reginald, P. W. Splenic rupture in utero following a road traffic accident. Case report 318
- Siddle, N. See MacDougall, J.
- Singer, A. See Szarewski, A.
- Singhal, V. See Li, T. C.
- Singhal, V., Li, T. C. & Cooke, D. An analysis of factors influencing the outcome of 232 consecutive tubal microsurgery cases 628
- Skajaa, K., Dørup, I. & Sandstrom, B. -M. Magnesium intake and status and pregnancy outcome in a Danish population 919
- Skajaa, K. See Eriksen, G.
- Skensved, H., Hansen, A. & Vetner, M. Immunoreactive endometritis 578
- Skerrow, S. M. See Taylor, P. V.
- Slack, J. See Marteau, T. M.
- Slevin, M. L. See Gallagher, G. J.
- Smith, D. E. See Kell, P. D.
- Smith, J. R. & Kitchen, V. S. Commentary Reducing the risk of infection for obstetricians 124
- Smith, J. R. Book review. *Infectious Diseases of the Female Genital Tract Second Edition* 235
- Smith, S. K. Correspondence. The future obstetrician/gynaecologist Commentary 841
- Snijders, R. J. M. See Thorpe-Beeston, J. G.
- Snijders, R. J. M. See Ribbert, L. S. M.
- Sokol, R. See Fraser, W. D.
- Sonnendecker, E. W. W. See Mitri, F. F.
- Soper, N. See Kennedy, S.
- Sørensen, J. D. See Secher, N. J.
- Sørensen, S. See Pedersen, J. F.
- Sørensen, F. B., Marcussen, N., Dagaard, H. O., Kristiansen, J. D., Møller, J. & Ingerslev, H. J. Immunohistological demonstrations of intermediate trophoblast in the diagnosis of uterine versus ectopic pregnancy: A retrospective survey and results of a prospective trial 463
- Soussis, I., Dimitry, E. S., Oskarsson, T., Margara, R. & Winston, R. Correspondence. Diagnosis of ectopic pregnancy by vaginal ultrasonography in combination with a discriminatory serum hCG level of 1000 IU/l (IRP) 233

- Soutter, W. P. Authors' reply 233
 Soutter, W. P. Commentary. Criteria for standards of management of women with an abnormal smear 1069
 Soutter, W. P. Computerization of a colposcopy clinic 824
 Soutter, W. P. Correspondence. The use of cervicography in a primary screening service 740
 Spehl, M. See Chanoine, J. P
 Spencer, J. See Kennedy, S
 Spencer, J. A. D. Book review *Medical Disorders During Pregnancy* 844
 Spencer, J. A. D., Nicolaides, P., Lee, A., Nicolini, U. & Rodeck, C. H. Short communication. Cervical preparation with gemeprost for dilatation and evacuation 731
 Spencer, K. Correspondence. First trimester CA 125 and Down's syndrome 946
 Spitz, B. See Hanssen, M
 Spowart, K. See Hawthorn, R. J. S.
 Srivastava, S. & Maxwell, R. Vulval reconstruction by free tissue transfer. Case report 98
 Stamatakis, J. D. See Stephenson, B. M
 Stanley, F. J. See Bryce, R. L.
 Stanton, S. L. See Creighton, S. M
 Steegers, E. A. P., Jongasma, H. W., Eskes, T. K. A. B., Hein, P. R., van Lakwijk, H. P. J. M., Fast, J. H., Symonds, E. M. & Godschalx, A. W. H. J. Correspondence. Atrial natriuretic peptide and atrial size during normal pregnancy 1188
 Steegers, E. A. P., van Lakwijk, H. P. J. M., Jongasma, H. W., Fast, J. H., De Boo, T., Eskes, T. K. A. B. & Hein, P. R. (Patho)physiological implications of chronic dietary sodium restriction during pregnancy: a longitudinal prospective randomized study 980
 Steegers, E. A. P., van Lakwijk, H. P. J. M., Fast, J. H., Godschalx, A. W. H. J., Jongasma, H. W., Eskes, T. K. A. B., Symonds, E. M. & Hein, P. R. Atrial natriuretic peptide and atrial size during pregnancy 202
 Steer, P. J. See Lamont, R. F
 Steer, P. J. See Paterson, C. M.
 Steer, P. J. See Penn, Z. J
 Stemers, N. See Koninx, P. R
 Stephenson, B. M. & Stamatakis, J. D. Short communication. Late recurrence of a congenital diaphragmatic hernia. Case report 110
 Stevenson, D. K. See Seidman, D. D
 Stevenson, J. C. See Crook, D.
 Stewart, A. Correspondence. Vitamin B6 in the treatment of the premenstrual syndrome—review 329
 Stewart, P. See Cohn, M.
 Stewart, P. Book review. *Baillière's Clinical Obstetrics and Gynaecology, International Practice and Research. Medical Induction of Abortion, Vol. 4, No. 2, June 1990* 615
 Sturatt, G. M. See Bisson, D. L.
 Sturatt, G. M. See Dwyer, N. A
 Stones, R. W. See Beard, R. W.
 Stronge, J. M. See Turner, M. J
 Studd, J. & Garnett, T. J. Authors' reply 503
 Studd, J. & Garnett, T. J. Authors' reply 608
 Sullivan, M. H. F. See Ahmed, Y
 Sullivan, M. H. F. See Khan, H
 Sultan, Y. See Bertault, D
 Sumner, D. See Goodman, J. D. S
 Sundaresan, V. See Ilbery, M
 Sutcliffe, N. P. See Fox, J. G
 Sutherst, J. R. See Moore, K. H
 Svanberg, B. See Hjalmarsen, A. I. M.
 Symonds, E. M. Book review *Legal Principles and Practice in Obstetrics and Gynaecology Vol. 1* 418
 Symonds, E. M. See Baker, P. N.
 Symonds, E. M. See Loudon, K. A
 Symonds, E. M. See Steegers, E. A. P
 Szarewski, A. & Cuzick, J. Authors' reply 741
 Szarewski, A., Cuzick, J., Edwards, R., Butler, B. & Singer, A. The use of cervicography in a primary screening service 313
 Szawarski, Z. Commentary. Abortion in Poland 1202
 Tang, M. H. Y. See King, P. A
 Tannirandorn, Y. See Arulkumaran, S
 Tannirandorn, Y. See Nicolini, U.
 Tasker, M., Verduijn, C. P., Bassett, C., Murray, K. & Thornton, J. Correspondence. A randomized controlled trial of early amniotomy 1059
 Tate, G. See Taylor, P. V
 Taylor, P. V., Maloney, M. D., Campbell, J. M., Skerrow, S. M., Nip, M. M. C., Parmar, R. & Tate, G. Autoreactivity in women with endometriosis 680
 Taylor, P. V., Skerrow, S. M. & Redman, C. W. G. Short communication. Pre-eclampsia and anti-phospholipid antibody 604
 Taylor, W. G. Correspondence. Early identification of placenta praevia 332
 Taylor, W. G., Walkinshaw, S. A., Farquharson, R. G., Fiskien, R. A. & Gilmore, I. T. Pregnancy in Cnigler-Najjar syndrome. Case report 1290
 Tchobroutsky, C. See Bertault, D.
 Tebbutt, H. See Hughes, S. J
 Templeton, A. See Mahmood, T. A
 Templeton, A. A. See Henshaw, R. C
 Templeton, A. A. See Mahmood, T. A.
 Templeton, A. A. See Urquhart, D. R.
 Templeton, A. Commentary. Gamete donations and anonymity 343
 Templeton, A., Henshaw, R. & Urquhart, R. Authors' reply 1312
 Templeton, A. A. Book review *The Johns Hopkins Handbook of In Vitro Fertilization and Associated Reproduction Technologies* 339
 Templeton, A. A. Book review *Clinical IVF Forum. Current Views in Assisted Reproduction* 338
 Ten Cate, J. W. See De Boer, K.
 ter Riet, G. See Kleijnen, J
 Thaler, I. See Weiner, Z
 Thin, R. N. See Furlonge, C. B
 Thomas, E. Book review *Clinical Gynaecology* 1191
 Thomas, E. J., Okuda, K. J. & Thomas, N. M. The combination of a depot gonadotrophin releasing hormone agonist and cyclical hormone replacement therapy for dysfunctional uterine bleeding 1155
 Thomas, L. See Mahmood, T. A.
 Thomas, N. M. See Thomas, E. J.
 Thomas, P. See Bisson, D. L.
 Thomas, P. G. See Fox, R.
 Thomas, T. H. See Macphail, S
 Thong, K. J. & Baird, D. T. Correspondence. Uterine rupture in midtrimester abortion. A complication of gemeprost vaginal pessaries and oxytocin. Case report 416
 Thornton, J. See Tasker, M
 Thorogood, D. J. See Peel, K. R.
 Thorogood, M., Mann, J., Murphy, M. & Vessey, M. Is oral contraceptive use still associated with an increased risk of fatal myocardial infarction? Report of a case-control study 1245
 Thorpe-Beeston, J. G., Nicolaides, K. H., Snyders, R. J. M., Felton, C. V., Vyas, S. & Campbell, S. Relations between the fetal circulation and pituitary-thyroid function 1163
 Tittinen, A. See Cacciatori, B
 Tiltman, A. See Pijnenborg, R
 Toffoletti, F. G. See Scrimin, F
 Toppet, V. See Chanoine, J. P.
 Torode, H., Griffiths, K. & Gill, R. Correspondence. Transvaginal pulsed Doppler ultrasound assessment of blood flow to the corpus luteum in IVF patients following embryo transfer 112
 Tovo, P. A., Palomba, E., Gabiano, C., Galli, L. & de Martino, M. Short communication. Human immunodeficiency virus type 1 (HIV-1) seroconversion during pregnancy does not increase the risk of perinatal transmission 940
 Tozzi, L. See Parazzini, F
 Tracanzan, G. See Scrimin, F.
 Treffers, P. E. See De Boer, K.
 Trehan, A. K. & Fergusson, I. L. C. Congenital afibrinogenemia and successful pregnancy outcome. Case report 722

- Trehan, A. K. & Fergusson, I. L. C. Short communication The flying squad—an expensive and potentially dangerous practice in modern obstetrics 1177
- Tremble, J. M. *See* Colley, N. V.
- Trichopoulos, D. *See* Kalandidi, A.
- Trudinger, B. J. *See* Cook, C. M.
- Trudinger, B. J., Cook, C. M., Giles, W. B., Ng, S., Fong, E., Connelly, A., Wilcox, W. Fetal umbilical artery velocity waveforms and subsequent neonatal outcome 378
- Tulloch, A. *See* Coulter, A.
- Turnbull, A. *See* Baumann, R.
- Turner, M. J., Flannelly, G. M., Wingfield, M., Rasmussen, M. J., Ryan, R., Cullen, S., Maguire, R. & Stronge, J. M. The miscarriage clinic: an audit of the first year 306
- Tyrell, S. Author's reply 415
- Tzonou, A. *See* Kalandidi, A.
- Uldbjerg, N. *See* Khan, H.
- Urquhart, D. R. & Templeton, A. A. Psychiatric morbidity and acceptability following medical and surgical methods of induced abortion 396
- Urquhart, R. *See* Templeton, A.
- Usherwood, M. McD. *See* Griffiths, M.
- Usherwood, M. McD. *See* Hughes, S. J.
- van Assche, A. *See* Pijnenborg, R.
- van Assche, F. A. *See* Hanssen, M.
- van Dalen, C. M. *See* Christiaens, G. C. M. L.
- van der Heijden, P. F. M., Kremer, J. A. M., Brownell, J. & Rolland, R. Lactation inhibition by the dopamine agonist CV202-502 270
- van Lakwijk, H. P. J. M. *See* Steegers, E. A. P.
- van Lijnschoten, G. & Havenith, M. Correspondence Early recurrent miscarriage histology of conception products 336
- van Lith, J. M. M., Mantingh, A., Beekhuis, J. R., de Bruijn, H. W. A. & Breed, A. S. P. M. Short communication First trimester CA 125 and Down's syndrome 493
- Van Os, H. C. *See* Schats, R.
- Vaughan, J. I., Warwick, R., Welch, C. R. & Letsky, E. A. Correspondence. Anti-Kell in pregnancy 944
- Vercruysse, L. *See* Pijnenborg, R.
- Verduijn, C. P. *See* Tasker, M.
- Versi, E., Cardozo, L., Anand, D. & Cooper, D. Symptoms analysis for the diagnosis of genuine stress incontinence 815
- Vessey, M. *See* Thorogood, M.
- Vetner, M. *See* Skensved, H.
- Vigneswaran, R. *See* McDonald, H. M.
- Villa, L. *See* Candiani, G. B.
- Ville, Y., Leruez, M., Giowaczower, E., Robertson, J. N. & Ward, M. E. The role of *Chlamydia trachomatis* and *Neisseria gonorrhoeae* in the aetiology of ectopic pregnancy in Gabon 1260
- Vinall, P. S. *See* Wilkinson, B. S.
- Vincent, C. A., Martin, T. & Ennis, M. Obstetric accidents. the patient's perspective 390
- Vincenti, A. C. *See* Howe, D. T.
- Visser, G. H. A. *See* Ribbert, L. S. M.
- Volpe, C. *See* Scrimin, F.
- Von Dem Borne, Kr. A. E. G. *See* Christiaens, G. C. M. L.
- Vyas, S. *See* Thorpe-Beeston, J. G.
- Wald, N., Cuckle, H., Wu, T. & George, L. Maternal serum unconjugated oestriol and human chorionic gonadotrophin levels in twin pregnancies: implications for screening for Down's syndrome 905
- Wald, N. J. *See* Cuckle, H. S.
- Wald, N. J. *See* Haddow, J. E.
- Walker, J. J. *See* Greer, I. A.
- Walker, J. J. *See* Fairlie, F. M.
- Walker, J. J. *See* Fox, J. G.
- Walker, J. J. *See* Krishnamurthy, S.
- Walkinshaw, S. A. *See* Taylor, W. G.
- Walsh, D. *See* Hawthorn, R. J. S.
- Walters, W. A. W. *See* Schofield, M. J.
- Wang, K. *See* Creighton, S. M.
- Ward, K. *See* Woodman, C. J. B.
- Ward, M. E. *See* Ville, Y.
- Wardle, P. G. *See* Fox, R.
- Warrell, D. Book review. *Functional Diagnosis of the Lower Urinary Tract* 507
- Warwick, R. *See* Vaughan, J. I.
- Wathen, N. C., Cass, P. L., Campbell, D. J., Kitau, M. J. & Chard, T. Early amniocentesis: alphafetoprotein levels in amniotic fluid, extraembryonic coelomic fluid and maternal serum between 8 and 13 weeks 866
- Watkinson, M. *See* Bhoopalam, P. S.
- Watson, H. *See* Bonney, R. C.
- Weaver, J. B. *See* Constantine, G.
- Weaver, J. *See* McCormack, M. J.
- Webster, J. *See* Shelton, K.
- Weindling, A. M. *See* Garden, A. S.
- Weiner, Z., Thaler, I., Ronen, N. & Brandes, J. M. Changes in flow velocity waveforms in umbilical and uterine artery following haemodialysis. Case report 1172
- Welch, C. R. *See* Vaughan, J. I.
- Welch, C. R. Correspondence. The future obstetrician/ gynaecologist 840
- Wells, M. *See* Rutherford, A. J.
- Westgate, J. & Greene, K. R. Correspondence. Comparison of the T/QRS ratio of the fetal electrocardiogram and the fetal heart rate during labour and the relation of these variables to condition at delivery 1057
- Wheeler, T. *See* Newbold, S.
- Wheeler, T. *See* Robinson, S. M.
- White, M. C. *See* Burrell, L. M.
- Whitehead, M. *See* Fraser, D.
- Whitehead, M. I. *See* Gangar, K.
- Whitlaw, A. Book review. *Infection in the Newborn Perinatal Practice* 422
- Whittle, M., Fairlie, F. & Ryan, G. Correspondence. Randomized comparison of routine vs highly selective use of Doppler ultrasound and biophysical scoring to investigate high risk pregnancies 415
- Whittle, M. J. Book review. *Atlas of Ultrasound Measurements* 746
- WHO Task Force on Oral Contraceptives. A multicentre study of coagulation and haemostatic variables during oral contraception: Variations with four formulations 1117
- Wigglesworth, J. S. Book review. *A Colour Atlas of Life Before Birth, Normal Fetal Development* 420
- Wigglesworth, J. S. Commentary. Quality of the perinatal autopsy 617
- Wilcox, W. *See* Trudinger, B. J.
- Wilkins, T. *See* Chua, S.
- Wilkinson, C., Gyaneshwar, R. & McCusker, C. Twin pregnancy in a patient with idiopathic long QT syndrome. Case report 1300
- Wilkinson, L. S. *See* Perry, I. J.
- Wilkinson, P. *See* Pusey, J.
- Wilkinson, R. *See* Macphail, S.
- Wilkinson, B. S., Batcup, G. & Vinall, P. S. Partial placenta membranacea 675
- Williams, D. R. *See* Woodman, C. J. B.
- Williams, M. *See* Murdoch, A. P.
- Wilson, E. *See* Crofts, S. L.
- Wilson, P. O. G. *See* Carter, P. G.
- Wingfield, M. *See* Turner, M. J.
- Winston, R. M. L. *See* Oskarsson, T.
- Winston, R. M. L. *See* Perks, N. F.
- Winston, R. *See* Soussis, I.
- Winston, R. M. L. & Margara, R. A. Microsurgical salpingostomy is not an obsolete procedure 637
- Winter, R. Book review. *Essential Medical Genetics. Third Edition* 616
- Winter, R. Book review. *Obstetric Genetics* 505
- Wise, B. G. *See* Cutner, A.
- Witters, K. *See* Koninckx, P. R.

1332 *Author index*

- Wladimiroff, J. W. *See* Schats, R
 Wohler, M. *See* Eriksen, G
 Wojnarowska, F. *See* Frith, P
 Wolman, W. -L. *See* Hofmeyr, G. J
 Woodman, C. J. B., Yates, M., Williams, D. R., Ward, K., Jordan, J. & Luesley, D. A randomized control trial of cervical spatulas 21
 Woolas, R. *See* Prys Davies, A
 Wright, C. S. W. *See* Paterson, C. M
 Wu, T. *See* Wald, N
 Yates, M. *See* Woodman, C. J. B
 Ylikorkala, G. *See* Kurki, T
 Ylostalo, P. *See* Cacciatore, B
 Yoong, A., Rugman, F. P. & Hay, C. R. M. Correspondence. Hormone implants and tachyphylaxis 500
 Young, K. R. *See* Roberts, L. J
 Young, L. *See* Kitchener, H. C.
 Yovich, J. L. *See* Lower, A. M.
 Zolse, G. Correspondence Psychiatric morbidity and acceptability following medical and surgical methods of induced abortion 1312

SUBJECT INDEX

- Abdominal
 delivery *See* Labour and delivery
 pregnancy *See* Pregnancy ectopic
- Abortion *See also* Miscarriage
 effect on subsequent pregnancy outcome, long-term controlled cohort study 1015
 first trimester
 comparative effects of gemeprost and mifepristone on cervical resistance 1025
 effect of mifepristone on cervical resistance, RCT 778
 in Poland, legal aspects, commentary 1201
 psychiatric morbidity and acceptability associated with surgical or medical methods 396, correspondence 1312
 recurrent miscarriage *See* Miscarriage
 risk factor for ectopic pregnancy, case-control study 207
 second trimester
 efficacy of gemeprost for cervical preparation 731
 induced by gemeprost associated with uterine rupture, correspondence 416
 spontaneous *See* Miscarriage
- Acetylcholinesterase (AChE) to butyrylcholinesterase (BuChE) ratio in amniotic fluid, differential diagnosis of fetal abnormalities 52
- AIDS, a cause of maternal death, case report 725
- Alpha-fetoprotein (AFP)
 levels in amniotic fluid, extraembryonic coelomic fluid and maternal serum between 8 and 12 weeks 866; commentary 849
 screening associated with cotinine-assisted intervention to reduce smoking 859
- Amenorrhoea *See* Menstrual cycle
- Amniotic fluid
 AChE to BuChE ratio, prognostic significance for fetal abnormalities 52
 AFP concentrations between 8 and 12 weeks gestation 866
 amniocentesis
 in first trimester for prenatal diagnosis, commentary 849
 uptake and attitudes in older women 282
 amniotomy, effect on duration of labour, RCT 84; correspondence 1059
 hydramnios associated with placental chorioangioma, case report 322
 low levels of oestriol and DHEAS with high hCG in Down's syndrome 1160
 polyhydramnios, acute recurrent, management with indomethacin, case report 583
 two tests for fetal lung maturity, two bedside indicators 479
- Amniotic membrane
 preterm prelabour rupture
 and amnionitis, diagnostic value of maternal serum CA 125 levels 835
 association with vaginal infection 427
 PGE₂ production, in vitro quantitative study 712
- Analgesia/Anaesthesia
 epidural in labour
 associated with transient impaired utero-placental circulation, Doppler study 1174
 in Takayasu's arteritis, case report 408
 pain relief in labour, long-term maternal consequences, commentary 1193; correspondence 333
- Androgen and oestrogen states in oligo-amenorrhoeic women with PCO disease 294
- Angiotensin II
 platelet binding sites in normotensive and hypertensive women 436
 positive pressor response in normotensive pregnancies with abnormal umbilical artery FVW 698
 sensitivity and supine pressor test, prediction of PIH, correspondence 231
 serum levels in hypertensive and normotensive pregnancies 155
- Antibodies/Antigens
 anticardiolipin levels in pre-eclamptic women 604, correspondence 1313
 anti-Kell in pregnancy, frequency and effect on outcome, 25-year survey 162, correspondence 943
 anti-platelet, prognostic marker in lupus nephritis, case reports 324
 anti-D prophylaxis for rhesus disease, costs in India 369, commentary 509 (erratum 1192)
 autoreactivity to nuclear, phospholipid and smooth muscle antigens in endometriosis 680
 CA 125 serum levels
 in pregnancy not diagnostic for amnionitis with preterm prelabour rupture of the membranes 835
 lower in Down's syndrome pregnancies 493; correspondence 946
 raised in carcinoma of the fallopian tube, two case reports 602
 HIV-1 seroconversion in pregnancy, effect on perinatal transmission 940
 maternal anti-Ro (SS-A) antibody, review of current management 751
 monoclonal JMB 2, cytokeratin marker, trophoblast deportation study 973
 overlap syndrome, effect on pregnancy outcome, case report 728
 screening for cytomegalovirus 135
 tumour markers, CEA, EMA, DD9 and CAM 5-2, localization in epithelial ovarian cancer 73
- Artificial insemination *See* Infertility
- Atrial natriuretic peptide and atrial size during normal pregnancy 202, correspondence 1188
- Audit *See also* Population studies
 in obstetrics, effects of, commentary 1065
 management of ectopic pregnancy 1267
 management of the preterm breech delivery 531
 mode of delivery, effect on cost of maternity care 519
 of colposcopy practice in the UK, postal questionnaire 1112
 perinatal autopsies from the 1987 West Midlands survey 624; commentary 617
 results of the first year in a miscarriage clinic 306
 review of the use of computer collected audit data in assessing the quality of maternity services 1073, commentary 1065
 workload in gynaecology, linked statistical data 772
- Avicenna's recipe for contraception, historical 1303
- Bacterial infections
 aetiological role of *C. trachomatis* and *N. gonorrhoea* in ectopic pregnancy in Gabon 1260
 pneumocystosis associated with maternal death caused by AIDS, case report 725
 reducing the risk of infection for obstetricians, commentary 125
 vaginal microflora effect on preterm prelabour rupture of the membranes 427
- Bile acids, serum levels in normal pregnancy, longitudinal study 540
- Birthweight
 correlation with ponderal index 527
 effect of smoking in pregnancy 859
 in relation to placental weight, effects of maternal anaemia and iron deficiency 886

- low birthweight associated with maternal stressful life events, population study 166
not related to maternal fat/weight gain 254
- Bladder**
detrusor instability, commentary on current management, correspondence 114
distal urethral electrical conductance—quick screening test for incontinence 69
effects of pregnancy on previous incontinence surgery, case report 1181
genuine stress incontinence, diagnostic accuracy of symptoms analysis 815
sensory urgency, maximum bladder capacity and individual perception of bladder fullness 1287
Stamey endoscopic bladder neck suspension, clinical and urodynamic study 1141
stress incontinence treated by colpo-needle suspension 1183
urinary symptoms in early pregnancy, urodynamic assessment 1283
voiding in crouching position, effect on urine flow rate and residual volume 569
- Blair Bell Research Society** abstracts 495, 1304
- Blood**
coagulation and haemostatic variables, effects of four different OC preparations, multicentre study 1117
- disorders**
congenital afibrinogenemia, case report of successful pregnancy 722
haemorrhagic problems in obstetrics and gynaecology in patients with congenital coagulopathies, 30-year review 909
HELLP syndrome, coagulation studies 42
idiopathic thrombocytopenic purpura in pregnancy, correspondence 334, 946
maternal anaemia and iron deficiency association with high ratio of placental to fetal weight 886
protein C deficiency associated with unfavourable pregnancy outcome, case reports 934
erythrocyte hydration *in vitro* in normal pregnancy 1205
flow Doppler velocity waveform studies *See* Ultrasound
- groups**
fetal Rh alloimmunization associated with liver dysfunction 287
rhesus haemolytic disease of the newborn, immunoprophylaxis in India 369; commentary 509 (erratum 1192)
- haemodynamic studies**
blood pressure at 17 years of age in relation to pre-eclampsia during mother's pregnancy 1009
blood pressure measurements in pregnancy, current practice 241; commentary 239; correspondence 342
effects of verapamil on vasodilatation and respiratory function in pre-eclampsia 964
vasoactive intestinal polypeptide plasma levels in pre-eclampsia 803
- orbital haematoma** developed during labour, case report 227
- platelets**
angiotensin II binding sites in hypertensive pregnancy 436
anti-platelet antibodies associated with lupus nephritis in pregnancy 324
reactivity in gestational hypertension and pre-eclampsia 1239
- vascular disease**, Takayasu's arteritis, epidural analgesia for labour, case report 408
venous congestion, cause of chronic pelvic pain, effect of oophorectomy and hysterectomy 988
- Bone**, acromegalic changes in severe polycystic ovarian disease, an effect of hyperinsulinaemia, case report 410
- Brain**, neonatal cerebral lesions associated with maternal trauma and preterm birth, case reports 1292
- Breech presentation** *See* Labour and delivery
- Bromocriptine** and CV205-502 (dopamine agonists), inhibitory effect on lactation 270
- Buserelin**, GnRH agonist, effect on IVF pregnancy rates 544
- Butyrylcholinesterase** to AChE ratio in amniotic fluid, differential diagnosis of fetal abnormalities 52
- CA 125** *See* Antibodies/Antigens
- Caesarean section** *See* Labour and delivery
- Calcium antagonist** verapamil, effect on respiratory function in pre-eclampsia 964
- Carcinoma** *See also* Tumours
- cervical**
CIN *See* Cervix
colposcopically directed punch biopsy, a potentially misleading investigation 1273
in women <40 years of age, 10-year regional survey 993
risk in nuns, virgins and spinsters, historical review 797; correspondence 1315
- endometrial/uterine**
incidental finding after endometrial resection, case report 733
recurrent, treatment with GnRH analogues 1037
- fallopian tube**, associated with raised serum CA 125 levels, case reports 602
- gestational trophoblastic tumours**, efficacy of EMA/CO chemotherapy 550
- ovarian**, epithelial, immunoperoxidase localization of tumour markers 73
- renal lymphoma** causing renal failure in pregnancy, case report 216
- Cervagem** *See* Gemeprost
- Cervicography**, use in a primary screening service 313; correspondence 740
- Cervix**
carcinoma
in women under 40 years of age, 10-year regional survey 993
risk in 'nuns, virgins and spinsters', historical review 797; correspondence 1315
cerclage, efficacy of emergency procedure, 3-year retrospective study 1234
- colposcopy**
clinic, benefits and difficulties of computerization 824
directed punch biopsy, a potentially misleading investigation 1273; correspondence 232; diagnostic efficacy 588
practice in the U.K., postal questionnaire audit 1112
- cytological screening**
RCT of two cervical spatulas 21, commentary 6
use of cervicography in a primary screening service 313; correspondence 740
what constitutes an adequate smear, commentary 6
- human papillomavirus infection**, prospective serial histological study and genome detection 1042
- intraepithelial neoplasia (CIN)**
associated with vaginal epithelial abnormalities, management 25
atypical transformation zone, lesion size and histology 490
CIN 3, effective destruction at 100°C with Semm cold coagulator, 14 years experience 14
colposcopically directed punch biopsy, a misleading investigation 1273
criteria for management of women with abnormal smears, commentary 1069
diagnostic efficacy of LLETZ compared with directed punch biopsy 588
treatment, do we need lasers, commentary 3
- preparation before abortion**
efficacy of gemeprost 731
effect of mifepristone pretreatment, RCT 778
effectiveness of gemeprost and mifepristone compared 1025
resistance in labour, PGE₂ effects 441, correspondence 1314
traction with a tenaculum effect on uterocervical angle 309
- Chlamydia trachomatis** *See* Bacterial infections
- Chorion villus sampling (CVS)**
in first trimester, commentary 849
trans-abdominal associated with infection and miscarriage, case report 413
- Chromosomes**
abnormalities, range and prevalence in failing pregnancies in subfertile women 1228

- HPV genome detection in infected cervix 1042
prenatal karyotyping in first trimester chorion villus sampling or amniocentesis, commentary 849
Cicatrical pemphigoid, ocular and vulval, case reports 483
Colposcopy *See* Cervix
Computer studies
 computerization of a colposcopy clinic, benefits and difficulties 824
 review of the use of computer-collected audit data in assessing quality of maternity services 1073; commentary 1065
Congenital abnormalities
 associated with maternal Crigler-Najjar syndrome, case report 1290
 coagulopathies associated haemorrhagic problems in obstetrical and gynaecological procedures, review 909
 Down's syndrome *See* Down's syndrome
 fast scan magnetic resonance imaging of fetal anomalies 1217
 fetal complete heart block associated with maternal anti-Ro (SS-A) antibody, review of management 751
 long QT syndrome in twin boys, case report 1300
 prognostic significance of AChE to BuChE ratio in amniotic fluid 52
Contraception
 Avicenna's recipe, historical 1303
 oral
 effects on coagulation and haemostasis, multicentre study of four different oestrogen and progestogen regimens 1117
 low-dose regimens, association with fatal myocardial infarction, case-controlled study 1245
 Corticotrophin-releasing hormone elevated in preterm labour, effect of indomethacin or nylidrin 685
 Cotinine-assisted intervention to reduce smoking in pregnancy 859; commentary 847
 Crigler-Najjar syndrome and pregnancy, case report 1290
 CV 205-502, dopamine agonist, inhibiting lactation 270
 Cytomegalovirus *See* Virus infections
Delivery *See* Labour and delivery
Diplopia after labour, case report 227
Dopamine agonists CV 205-502, inhibitory effect on lactation 270
Doppler ultrasound *See* Ultrasound
Down's syndrome
 associated with low levels of oestriol and DHEAS but high hCG levels in amniotic fluid 1160
 associated with lower maternal serum CA 125 levels 493; correspondence 946
 maternal serum levels of unconjugated oestriol and hCG levels in twin pregnancies 905
Dysmenorrhoea *See* Menstrual cycle
Eclampsia *See also* Pre-eclampsia
 postpartum and renal failure, treatment with prostacyclin, case report 400; correspondence 1055
Ectopic pregnancy *See* Pregnancy ectopic
Education/Training
 obstetrics and gynaecology practice litigation, commentary 423; correspondence 1185
 the future obstetrician/gynaecologist, commentary 237; correspondence 840
 undergraduate obstetrics and gynaecology, 1989 survey 127, commentary 121
 usefulness of obstetric audits, commentary 1065
Endometriosis
 association with autoreactivity to nuclear, phospholipid and smooth muscle antigens 680
 benign polyclonal lymphoid proliferation, histological study 578
 pelvic, associated menstrual symptoms, survey questionnaire 559
 pulmonary, imaging by immunoscintigraphy, case report 600
 renal treatment with GnRH agonist, case report 406
 role in infertility
 effect on follicular development in spontaneous and stimulated cycles 783
 oocyte and follicular fluid characteristics 573
 peritoneal fluid volume and concentration of sex steroids during menstrual cycle 179
Endometrium *See also* Uterus
 carcinoma
 incidental finding after endometrial resection, case report 733
 recurrent, therapeutic effect of GnRH analogues 1037
 cytological assessment in management of postmenopausal bleeding 488
 effects of long-term continuous HRT 939
 immunoreactive endometritis histological study 579
 Nd-YAG laser ablation for menorrhagia, multicentre clinical study 357
 response to HRT in premature ovarian failure, histological aspects 656
 thickness in postmenopausal women, vaginal sonography 470
 tissue sampling, use of Gynoecheck, correspondence 115
 resection
 for menorrhagia, review of 80 procedures 1049
 hysteroscopic, patient selection 228; correspondence 839; 948
 identification of early carcinoma, case report 733
Elastase
 containing neutrophils at the materno-fetal interface in PIH 929
 neutrophil elevated in SGA pregnancies 105
Epidemiology *See* Population studies
Ethinamate and mefenamic acid, therapy for menorrhagia 707
Eye
 catratrical pemphigoid associated with vulval disease, case reports 483
 diplopia after labour, case report 227
Fallopian tubes
 carcinoma associated with raised serum CA 125 levels, case reports 602
 management of ectopic pregnancy, comparison of videopelviscopy with laparotomy 765
 tubal infertility treatment
 factors affecting outcome of microsurgery 628
 results of microsurgical salpingostomy in 388 women 637; commentary 619, correspondence 1309
 tubal patency testing, clinical comparison of sonographic hydrotubation and hysterosalpingography 1031
 value of salpingoscopy, correspondence 332
 tuboscopy in reversal of sterilization 327
Fertility *See* Infertility
Fertilization in vitro *See* in vitro fertilization
Fetal
 abnormalities *See also* Congenital abnormalities
 bowel atresia following gastroschisis, case report 214
 complete congenital heart block associated with maternal connective tissue disease, review 751; maternal overlap syndrome, case report 728
 Down's syndrome, antenatal screening 905, associated with lower maternal serum CA 125 levels 493; correspondence 946
 hydropic fetuses associated with liver dysfunction 287
 identification by fast scan magnetic resonance imaging 1217
 liver dysfunction in Rh alloimmunization 287
 pleural effusions, spontaneous variation, case report 403
 splenic rupture following a motor accident, case report 318
 antenatal care *See* Pregnancy management
 birthweight *See* Birthweight
 blood flow, Doppler studies
 descending aorta and middle cerebral artery, changes in FVW associated with changes in thyroid concentrations 1163
 umbilical artery FVW, absent end diastolic flow associated with normal neurobehaviour 277, predictive value for outcome 378, 956; RI changes associated with maternal haemodialysis, case report 1172

- uteroplacental circulation: abnormal FVW associated with placental abruption 225, effect on outcome in high-risk pregnancies 956
- blood sampling, cordocentesis
 - and miscarriage in relation to indication 892
 - for diagnosis of congenital toxoplasmosis 832; correspondence 1311
 - continuous monitoring with electrocardiographic waveform analysis 829
- breathing, predictive value for lethal pulmonary hypoplasia and chorioamnionitis, pilot study 692
- chorion villus sampling for screening in first trimester, commentary 849; trans-abdominal associated with infection and miscarriage 413
- growth assessment
 - crown-rump length values in first trimester using abdominal scans 48; vaginal sonography 460; correspondence 946
 - SGA fetuses associated with increased neutrophil activation 105; role of stressful life events 166
 - IUGR screening, midtrimester uteroplacental Doppler blood flow studies 871
 - value of ponderal index 527
- heart activity
 - direct antenatal fetal echocardiographic waveform analysis 829
 - rate in early and late pregnancy, relation to size at birth 1223
 - reproducibility of echocardiographic measurements 807
- heart rate pattern
 - and T/QRS ratio of the ECG in relation to outcome 173
 - correlated with umbilical blood PO₂ values 820
 - variation and fetal blood gases in SGA fetuses 820
 - pseudo-sinusoidal pattern in labour, prevalence and clinical significance 1097
- injury
 - fatal seat belt injury during motor accident, case reports 320
 - splenic rupture following a motor accident, case report 318
- intrapartum monitoring
 - efficacy of pulse oximetry 36
 - role in obstetric accidents, the patient's perspective 390, correspondence 945
- liver enzymes abnormality in Rh alloimmunization 287
- membranes, PGE₂ production, in vitro quantitative study 712
- outcome *See* Newborn
- prenatal diagnosis/screening
 - AFP levels between 8 and 12 weeks gestation 866
 - chorion villus sampling or amniocentesis, commentary 849
 - cordocentesis and pregnancy loss in relation to indication 892
 - cordocentesis for congenital toxoplasmosis 832, correspondence 1311
 - differential diagnostic value of amniotic fluid ratio of AChE to BuChE 52
 - lung maturity, reliability of two rapid bedside tests using amniotic fluid 479
 - use of fast scan magnetic resonance imaging 1217
- tests of well-being
 - comparison of routine vs selective biophysical profile scoring and FVWs, correspondence 415
 - direct electrocardiographic waveform analysis 829
 - neurobehavioural development normal in association with absent umbilical artery end diastolic velocity 277
 - predictive value of umbilical artery FVW studies 378
 - pulse oximetry 36
 - relation between FHR pattern variation and fetal blood gases in SGA fetuses 820
- Fibroids, risk of recurrence after myomectomy 385
- Fish-oils effect on pre-eclampsia, correspondence 499, 737
- Flying Squad
 - organization and responsibilities, commentary 1067, case reports 1177
- Follicular development in women with minimal-mild endometriosis 573, 783
- Galactorrhoea and growth hormone excess without acromegaly, case reports 92
- Gastrointestinal tract
 - congenital diaphragmatic hernia, late recurrence in pregnancy, case report 110
 - fetal bowel atresia following gastroschisis, case report 214
 - serum bile acids in normal pregnancy, longitudinal study 540
- Gemeprost
 - compared with mifepristone for cervical priming before abortion 1025
 - effect on cervical preparation for abortion 731
 - in midtrimester abortion associated with uterine rupture, correspondence 416
- Genetic studies
 - mechanism for susceptibility to pre-eclampsia, model study 1079
- Gestational age *See* Pregnancy gestational age
- Gestational trophoblastic tumours, efficacy of EMA/CO chemotherapy 550
- Gonadotrophins
 - GnRH agonists
 - buserelin, effect on IVF pregnancy rates 544
 - goserelin plus HRT for menorrhagia 1155
 - leuporelin and goserelin, treatment for recurrent endometrial cancer 1037
 - nafarelin, treatment in renal endometriosis, case report 406
 - human chorionic gonadotrophin (hCG)
 - excretion in early pregnancy, absence of diurnal variation 1180
 - levels for early pregnancy dating, correspondence 330
 - low amniotic fluid levels in Down's syndrome 1160
 - maternal serum levels in twin pregnancy 905
 - lutinizing hormone (LH) pulse pattern in PCO disease 300
- Goserelin
 - plus HRT therapy for menorrhagia 1155
 - treatment for recurrent endometrial cancer 1037
- Growth hormone excess and galactorrhoea without acromegalic features, case reports 92
- Gynaecology
 - audit of workload using linked statistical data 772
 - outcomes of referrals for menstrual problems, an audit of general practice records 789
- Gynoecheck, endometrial tissue sampler, correspondence 115
- Heart
 - antenatal fetal electrocardiographic waveform analysis 829
 - atrial natriuretic peptide and atrial size during normal pregnancy 202, correspondence 1188
 - congenital heart block associated with maternal overlap syndrome 728
 - fatal myocardial infarction, associated with low-dose OC regimens, case-control retrospective study 1245
 - fetal cardiac haemodynamics, reproducibility of ultrasound measurement 807
 - maternal idiopathic long QT syndrome associated with successful twin pregnancy, case report 1300
 - T/QRS ratio of fetal ECG, relation to FHR pattern during labour 173, correspondence 1057
- HELLP syndrome in pregnancy, coagulation study 42
- Hepatitis *See* Virus infection
- Histoacryl, use for episiotomy repair 476; correspondence 1315
- Historical reviews
 - aspects of toxemia in pregnancy 853
 - Avicenna's recipe for contraception 1303
 - Rigoni-Stern and cervical cancer in 'nuns, virgins and spinsters' 797; correspondence 1315
- Hormone replacement therapy (HRT)
 - associated with haematometra, case report 837
 - combined regimens, effect on lipid metabolism, commentary 749
 - cyclical in association with depot GnRH agonist for treatment of menorrhagia 1155
 - endometrial response in premature ovarian failure 656

- hormone implants and tachyphylaxis, correspondence 500, 607
- induced withdrawal bleeds quantified 106
- long-term continuous combined regimen, effect on endometrial status 939
- Human immunodeficiency virus (HIV) *See* Virus infections
- Hydatidiform mole, results with the EMA/CO regimen in high-risk gestational trophoblastic tumours 550
- Hydralazine intravenous, effect on umbilical artery FVW in hypertensive pregnancy 453; correspondence 1187
- Hypertensive pregnancy *See also* Pre-eclampsia
 - angiotension II serum levels 155
 - HELLP syndrome, coagulation study 42
 - immunocytochemical localization of neutrophil elastase in term placenta decidua and myometrium 929
 - increased platelet turnover with failure of aspirin therapy, case report 218
 - intensive antihypertensive therapy to prevent pre-eclampsia, RCT 244
 - maternal and fetal haemodynamic effects of intravenous labetalol and hydralazine 453, correspondence 1187
 - placental bed spiral arteries, histological study 648; commentary 1195
 - platelet angiotensin II binding sites 436
 - platelet reactivity in whole blood 1239
 - prediction by angiotensin II sensitivity and supine pressor test, correspondence 231
 - respiratory function, effects of rapid volume expansion with dextran and vasodilatation with verapamil 964
 - some historical aspects of toxemia in pregnancy, review 853
- Hysterectomy
 - and oophorectomy, treatment for chronic pelvic pain due to venous congestion 988
 - early postoperative mortality, Danish survey 147
 - self-reported long-term outcomes, Australian survey 1129
 - vaginal, combined with prophylactic oophorectomy in 1440 postmenopausal women 662
 - vaginal vault prolapse, surgical management, review 1150
- Hysteroscopy
 - endometrial resection, patient selection 228; correspondence 839; 948
 - Nd-YAG laser ablation of the endometrium for menorrhagia, multicentre clinical study 357
- Immunological studies
 - antenatal and neonatal screening for cytomegalovirus in a London population 135
 - anti-Kell in pregnancy, frequency and effect on outcome, 25-year survey 162; correspondence 943
 - anti-platelet antibodies: a prognostic marker in pregnancies associated with lupus nephritis, case reports 324
 - autoimmune ovarian failure, correspondence 115
 - IgA deficiency associated with vulvodynia, case reports 592
 - immunoperoxidase localization of tumour markers in ovarian cancer 73
 - immunoprophylaxis for rhesus disease, cost-effectiveness in India, 369, commentary 509 (erratum 1192)
 - immunoreactive endometritis, histological study 578
 - immunoscintigraphic imaging of pulmonary endometriosis, case report 600
 - overlap syndrome in pregnancy, case report 728
- Incontinence urinary *See* Bladder
- Indomethacin
 - no effect on CRH levels in preterm labour 685
 - treatment for recurrent polyhydramnios, case report 583
- Infertility
 - due to anovulatory POD, treatment with laparoscopic ovarian electrocautery 30
- gamete donation and anonymity, commentary 343; population survey 351
- in minimal-mild endometriosis, no effects on follicular development 783
- subfertile women, subsequent obstetric and neonatal outcome, cohort study 1087
- tubal
 - factors affecting outcome of 232 microsurgical operations 628, correspondence 1309
 - management in the 1990s, commentary 619, correspondence 1309
 - results of microsurgical salpingostomy in 388 women 637, commentary 619, correspondence 1309
 - vaginal sonographic hydrotubation for patency testing 1031
 - value of salpingoscopy, correspondence 332
- In vitro fertilization (IVF)
 - blood flow to corpus luteum, transvaginal pulsed Doppler study, correspondence 112
 - gamete donation and anonymity, commentary 343; attitudes of IVF participating couples, postal questionnaire 351
 - pregnancy rates
 - buserelin as affecting, RCT 544
 - cumulative after GIFT 643
 - GIFT compared with intrauterine insemination, 59 couples 1107
 - range and prevalence of chromosome abnormalities in failing pregnancies 1228
 - superovulation associated with ovarian necrotizing vasculitis with haemorrhage, case report 596
- Insulin elevated levels associated with ovarian failure, correspondence 115
- Iron deficiency in pregnancy associated with high ratio of placental to fetal weight 886
- Kidney
 - renal endometriosis, treatment with GnRH agonist, case report 406
 - renal failure with postpartum eclampsia, prostacyclin therapy, case report 400, correspondence 1055
 - renal lymphoma causing renal failure in pregnancy, case report 216
 - transplant recipient, maternal haemodialysis associated with improved Doppler fetal velocimetry findings, case report 1172
- Labetalol, intravenous, effect on umbilical artery FVW in hypertensive pregnancy, 453, correspondence 1187
- Labour and delivery
 - birth before arrival at hospital, prevalence and associated morbidity 57
 - breech presentation
 - effect of mode of delivery on neonatal mortality 898
 - external cephalic version at term, RCT 8, commentary 1, correspondence 839
 - preterm delivery, survey of management practice 531
 - caesarean section
 - effect on neonatal mortality in breech presentations, 17 587 infants 898
 - effect on perinatal mortality in low birthweight twins, case-control study 249
 - elective section after two CS, commentary 1199
 - postnatal x-ray pelvimetry, role in management of subsequent deliveries 716
 - scar rupture after previous lower uterine segment CS, role of uterine activity measurements 265
 - complications
 - birth asphyxia, definition and prevention, commentary 953
 - diplopia after labour, case report 227
 - obstetric accidents, the patient's perspective 390; correspondence 945
 - partial placenta membranacea 675
 - placenta accreta and myotonic dystrophy, case reports 594
 - postpartum eclampsia and acute renal failure, treatment with prostacyclin, case report 400, correspondence 1055
 - postpartum haemorrhage, atonic, controlled with intra-myometrial 15m-PGF_{2α} 743; in women with congenital coagulopathies, 30-year review 909
 - retained placenta, management by umbilical vein injection, commentary, 348
 - slow progress associated with insufficient remodelling of uterine connective tissue 1212

- duration of labour, effect of early amniotomy, RCT 84, correspondence 1059
- effect of caput succedaneum on SO_2 measurements, correspondence 113
- induced labour, intrauterine pressures monitored 441, correspondence 1314
- intrapartum monitoring
 - ECG recordings, T/QRS ratio and FHR in relation to outcome 173; correspondence 1057
 - pseudo-sinusoidal FHR pattern, prevalence and relation to outcome 1093
 - pulse oximetry 36, effect of caput succedaneum, correspondence 113
- episiotomy repair, use of Histoacryl 476, correspondence 1315
- management
 - epidural analgesia in Takayasu's arteritis 408
 - in developing countries, commentary 345, correspondence 841
 - in women with spinal cord injuries 513
 - of retained placenta by umbilical vein injection, commentary 348
 - pain relief, correspondence 333
 - social support companionship, effects on labour and breastfeeding, RCT 756
 - the flying squad, organization and responsibilities, commentary 1067; case reports 1177
 - third stage management, oxytocin, sulprostone and placebo compared, RCT 528
- mode of delivery (other than CS)
 - advantages of an obstetric birth chair, RCT 657
 - effect on the cost of maternity care 519
 - instrumental, maternal response to forceps or the silc-cup 487
 - management after previous CS, role of x-ray pelvimetry 716
 - vaginal delivery is possible after two CS, commentary 1199
- perinatal transmission of hepatitis B, prevention and control 141
- placental abruption
 - associated factors, case-control study 448
 - preceded by abnormal uterine artery FVW, case report 225
- preterm labour
 - associated vaginal microflora 427
 - associated with elevated maternal plasma CRH levels, no effect of indomethacin or nylidrin 685
 - in breech presentation, survey of management practice 531
 - prelabour rupture of membranes not associated with raised CA 125 levels 835
 - preventive effect of antenatal social support, RCT 1001
 - survey of women's health after childbirth, commentary 1193
- uterine activity
 - in trials of scar associated with scar rupture, retrospective study 265
 - patterns in induced and spontaneous labours 441; correspondence 1314
- Lactation
 - breast feeding improved by social support during labour, RCT 756
 - inhibition by CV 205-502, a dopamine agonist 270
 - response to nasal administration of thyrotrophin-releasing hormone 880
- Laparoscopic management of ectopic pregnancy 765; retrospective review 1254
- Laser
 - CO_2 laparoscopic treatment of ectopic pregnancy, retrospective review 1254
 - Nd-YAG laser ablation of the endometrium for menorrhagia, multicentre study 357
 - treatment for CIN, commentary 3
- Leiomyoma *See* Fibroids
- Leuporelin and goserelin treatment for recurrent endometrial cancer 1037
- Lichen sclerosis, vulval reconstruction by free tissue transfer, case report 98, correspondence 613
- Lipid metabolism, effect of menopausal combined HRT regimens, commentary 749
- Ligation
 - in obstetrics and gynaecology, commentary 423; correspondence 1185
 - patient's perspective of obstetric accidents 390; correspondence 945
- Liver
 - fetal liver dysfunction in rhesus alloimmunization 287
 - function, serum bile acids in normal pregnancy, longitudinal study 540
 - perinatal transmission of hepatitis B, prevention and control 141
 - transplant recipient, pregnancy management and outcome, case report 719
- Lungs
 - fetal lung maturity estimation in amniotic fluid, reliability of two rapid bedside tests 479
 - fetal pleural effusions, spontaneous variation, case report 403
 - lethal pulmonary hypoplasia, predictive value of breathing movements, pilot study 692
 - pulmonary endometriosis, imaging by immunoscintigraphy, case report 600
- Luteinizing hormone *See* Gonadotrophins
- Lupus nephritis in pregnancy associated with anti-platelet antibodies, case reports 324
- Magnesium intake and status effect on pregnancy outcome, Danish population 919
- Magnetic resonance imaging (MRI) fast scan imaging of fetal anomalies 1217
- Maternity services
 - quality assessment, use of computer collected audit data 1073; commentary 1065
 - reducing the risk of infection for obstetricians, commentary 125
 - The Flying Squad, use in modern obstetrics, case reports 1177, organization and responsibilities, commentary 1067
 - training for the future obstetrician/gynaecologist, commentary 237; correspondence 840
- Mefenamic acid and ethamsylate, therapy for menorrhagia 707
- Menopause
 - endometrial thickness in postmenopause estimated with vaginal sonography 470
 - hormone replacement therapy (HRT)
 - continuous combined HRT, effect on endometrial status 939, effect on lipid metabolism, commentary 749
 - implants and tachyphylaxis, correspondence 500, 607
 - induced withdrawal bleeds quantified 106
 - postmenopausal bleeding, endometrial biopsy and outpatient management 488
 - premature, endometrial response to HRT 656
- Menorrhagia *See* Menstrual cycle
- Menstrual cycle
 - associated changes in oestradiol receptor-related protein in skin 1277
 - blood loss measurements
 - effect on management in women with subjective excessive loss 326
 - of HRT-induced withdrawal bleeds in postmenopausal women 106
 - disorders, outcomes of referrals to gynaecology outpatient clinics, an audit of general practice 789
- menorrhagia
 - associated with higher endometrial phospholipase activity 363
 - review of 80 endometrial resections 1049
 - safety and clinical effectiveness of Nd-YAG laser ablation of the endometrium, multicentre study 357
 - therapeutic effects of ethamsylate and mefenamic acid compared 707
 - treatment in women with congenital coagulopathies, 30-year review 909

- treatment with depot GnRH agonist and cyclical HRT 1155
- menstrual symptoms in women with pelvic endometriosis, questionnaire survey 559
- oligo-amenorrhoea in PCO disease, oestrogen and androgen states 294
- premenstrual syndrome, vitamin B therapy, correspondence 329
- Mifepristone**
 - compared with gemeprost for cervical priming before abortion 1025
 - pretreatment, effect on cervical resistance before abortion 778
- Miscarriage (spontaneous abortion)**
 - after trans-abdominal CVS followed by infection, case report 413
 - counselling clinic, audit of the first-year results 306
 - diagnostic value of immunohistological demonstrations of hPL 463
 - early recurrent, histological study, correspondence 336
 - in twin pregnancy, retention of the second twin and livebirth, case reports 1295
 - placental bed biopsies, morphology and immunology, correspondence 609
 - rate after fetal blood sampling related to indication 892
- Molar pregnancy** *See* Hydatidiform mole
- Monoclonal antibodies** *See* Antibodies
- Mortality**
 - maternal
 - caused by AIDS, case report 725
 - in developing countries, commentary 345; correspondence 841
 - neonatal, effects of caesarean section in breech presentation, 17 587 infants 898
 - perinatal
 - due to rhesus (D) alloimmunization, commentary 509 (erratum 1192)
 - in twins < 2500 g birthweight, CS as affecting, case-control study 249
 - quality of perinatal autopsy, commentary 617
 - rates, babies born before arrival at hospital 57
 - the 1987 West Midlands survey, audit of 300 autopsies 624, commentary 617
 - the patient's perspective of obstetric accidents 390; correspondence 945
 - post-hysterectomy rates, Danish survey 147
- Multiple pregnancy** *See also* Twin pregnancy
 - trends in multiple births between 1955 and 1983 in Italy 535
- Myotonic dystrophy** associated with placenta accreta, case reports 594
- Nafarelin (GnRH analogue)** treatment in renal endometriosis, case report 406
- Natriuretic peptide**, atrial and atrial size during pregnancy 202; correspondence 1188
- Needle stick injury** reducing the risk of infection for obstetricians, commentary 125
- Neisseria gonorrhoeae*** *See* Bacterial infections
- Neodymium-YAG laser** ablation of the endometrium for menorrhagia, multicentre study 357
- Neutrophil activation** increased in SGA pregnancies 105
- Newborn**
 - abnormalities associated with maternal Crigler-Najjar syndrome, case report 1290
 - acidosis, prognostic significance of T/QRS ratio of fetal ECG in labour 173; correspondence 1057
 - anthropometric measurements, relation to FHR in early and late pregnancy 1223
 - birth asphyxia, definition and prediction, commentary 953
 - caput succedaneum effect on SO_2 measurements, correspondence 113
 - cerebral lesions in preterm infants associated with maternal trauma, case reports 1292
 - complete heart block associated with maternal overlap syndrome 728
 - enlarged thyroid associated with maternal smoking 65
 - growth assessment, relation between head/abdominal circumference ration, ponderal index and fetal malnutrition 524
 - haemolytic disease, costs of immunoprophylaxis in India 369, commentary 509 (erratum 1192)
 - haemolytic disease due to anti-Kell, 25-year survey 162, correspondence 943
 - lethal pulmonary hypoplasia, predictive value of fetal breathing 692
 - neonatal mortality, effect of mode of delivery in breech presentation 898
 - neonatal outcome after previous infertility, cohort study 1087
 - perinatal transmission
 - of hepatitis B infection, prevention and control 141
 - of HIV-1 after maternal seroconversion 940
 - serological screening for cytomegalovirus 135
- Nutrition**
 - chronic sodium restriction in pregnancy, physiological aspects 981
 - fish-oil in pregnancy, effect on pre-eclampsia, correspondence 499, 737
 - iron deficiency and anaemia in pregnancy association with high ratio of placental to fetal weight 886
 - magnesium intake and status, effect on pregnancy outcome, Danish population 919
 - maternal fat gain not related to birthweight 254
- Nylidrin**, no effect on CRH levels in preterm labour 685
- Obstetric practice**
 - patient's perspective of obstetric accidents 390, correspondence 945
 - reducing the risk of infection for obstetricians, commentary 125
- Oestrogens**
 - and androgen states in oligo-amenorrhoeic women with PCO disease 294
 - oestradiol
 - receptor-related protein, presence in skin and changes during menstrual cycle 1277
 - serum levels associated with HRT implants, correspondence 500, 607
 - oestriol
 - amniotic fluid levels in Down's syndrome 1160
 - unconjugated maternal serum levels in twin pregnancy 905
- Oocyte and follicular fluid** characteristics in mild endometriosis 573
- Ovary**
 - autoimmune failure, correspondence 115
 - blood flow, Doppler assessment after IVF, correspondence 112
 - epithelial cancer, immunoperoxidase localization of tumour markers 73
 - necrotizing vasculitis with haemorrhage after IVF, case report 596
 - polycystic ovarian disease (PCO)
 - associated with acromegalic bone changes and hyperinsulinaemia, case report 410
 - hormonal pulse patterns investigated 300
 - oestrogen and androgen states in oligo-amenorrhoea 295
 - treatment by laparoscopic ovarian electrocautery 30
 - premature failure and response to HRT 656
 - prophylactic vaginal oophorectomy combined with vaginal hysterectomy 662
 - theca-lutein cysts associated with placental chorioangioma, case report 322
- Pain relief** *See* Analgesia
- Papillomavirus** *See* Virus infections
- Pelvis** *See also* Abdomen
 - chronic pain due to pelvic congestion, effects of bilateral oophorectomy and hysterectomy 988
 - fetal splenic rupture in utero following a traffic accident, case report 318

- menstrual symptoms associated with pelvic endometriosis, questionnaire survey 559
- peritoneal fluid volume and levels of sex steroids in the pre-ovulatory period in mild endometriosis 175
- role of postnatal x-ray pelvimetry after CS in management of subsequent delivery 716
- Peptides vasoactive intestinal polypeptide plasma levels in pre-eclampsia 803
- Perinatal mortality *See* Mortality
- Phospholipase, endometrial activity elevated in menorrhagia 363
- Pituitary tumour, growth hormone excess and galactorrhoea without acromegaly, case reports 92
- Placenta
 - abruption
 - associated factors, a case-control study 448
 - preceded by abnormal uterine artery FVW, case report 225
 - accreta and myotonic dystrophy, case reports 594
 - bed biopsies in miscarriage, morphological and immunological study, correspondence 609
 - bed spiral arteries in hypertensive pregnancy, histological study 648; commentary 1195
 - chorioangioma associated with theca-lutein ovarian cyst, case report 322
 - chorion villus sampling in first trimester, commentary 849
 - haemochorial placenta, role in pregnancy success, commentary 1195
 - partial placenta membranacea 675
 - praevia, early identification, correspondence 332, 499
 - presence of neutrophil elastase in PIH pregnancies 929
 - retained, management by umbilical vein injection, commentary 348
 - trophoblast deportation into maternal circulation in pre-eclampsia 973
 - uteroplacental Doppler blood flow studies in second trimester, screening for IUGR and pre-eclampsia 871
 - weight in relation to birthweight, effects of maternal anaemia and iron deficiency 886
- Placental proteins
 - PP-14 low serum levels associated with ectopic pregnancy, brief report 414
 - placental lactogen, immunohistological demonstration to differentiate uterine and ectopic miscarriage 463
- Pneumocystis carinii* pneumonia associated with maternal death caused by AIDS, case report 725
- Polycystic ovaries *See* Ovary
- Population studies/Epidemiology
 - abortion, contraception and smoking as risk factors for ectopic pregnancy, case-control study, Greece 207
 - abortion in Poland, legal aspects, commentary 1201
 - antenatal social support effect on preterm birth, RCT 1001
 - attitudes towards gamete donation among couples undergoing in vitro fertilization 351
 - audits/surveys *See also* Audit
 - 10-year regional survey of cervical cancer in women <40 years 993
 - early post hysterectomy mortality 147
 - general practice records, outcomes of referrals to outpatient clinics for menstrual problems 789
 - menstrual symptoms associated with pelvic endometriosis, questionnaire study 559
 - obstetric management of the preterm breech 531
 - of workload in gynaecology, analysis of time trends from linked statistics 772
 - obstetric accidents, the patient's perspective 390, correspondence 945
 - perinatal mortality, West Midlands 624
 - self-reported long-term outcomes of hysterectomy, postal survey Australia 1129
 - undergraduate obstetrics and gynaecology 127; commentary 121
 - women's health after childbirth, commentary 1193
 - coagulation and haemostatic effects of four different oral contraceptive preparations, multicentre study 1117
 - cost of maternity care, effect of mode of delivery 519
 - cotinine-assisted intervention to reduce smoking in pregnancy in association with AFP screening 859; commentary 847
 - fibroids, risk of recurrence after myomectomy 385
 - Mg intake and status, effect on pregnancy outcome, Denmark 919
 - maternal mortality in developing countries, commentary 345; correspondence 841
 - mode of delivery and neonatal death in 17 587 infants presenting by the breech 898
 - psychiatric morbidity and acceptability following medical and surgical methods of induced abortion 396, correspondence 1312
 - role of stressful life events on birthweight 166
 - screening
 - cervical screening programmes and subsequent management, commentary 1069
 - controlling rhesus haemolytic disease of the newborn in India 369; commentary 509 (erratum 1192)
 - for cervical cancer in nuns, historical review 797; correspondence 1315
 - for Down's syndrome 905
 - efficacy of cervical smears, commentary 6
 - RCT of two cervical spatulas 21, commentary 6
 - serological screening for cytomegalovirus, London population 135
 - use of cervicography in a primary cervical screening service 313, correspondence 740
 - social support during labour effect on progress and breastfeeding, RCT 756
 - the Flying Squad, organization and responsibilities, commentary 1067; case reports 1177
 - trends in multiple births, 1955-1983 in Italy 535
 - women's attitudes to prolonged pregnancy, before and after term 1102
- Postmenopause *See* Menopause
- Pre-eclampsia *See also* Hypertensive pregnancy
 - and fish-oil supplementation, correspondence 499, 737
 - anti-phospholipid antibody serum levels, short report 604, correspondence 1313
 - associated with terminal pattern in fetal middle cerebral artery FVW, case report 937
 - genetic susceptibility, model study 1079
 - increased platelet turnover associated with failure of aspirin therapy, case report 218
 - influence on blood pressure, physique and intelligence in offspring at 17 years of age 1009
 - placental bed spiral arteries, histological study 648, commentary 1195
 - plasma levels of vasoactive intestinal polypeptides increased, prospective clinical study 803
 - platelet reactivity in whole blood 1239
 - prevention by intensive antihypertensive therapy 244
 - respiratory function, effects of volume expansion and vasodilatation with verapamil 964
 - screening by uteroplacental Doppler blood flow 871
 - some histological aspects of toxemia of pregnancy, review 853
 - trophoblast deportation into maternal circulation using monoclonal antibody JMB2 labelling 973
- Pregnancy
 - accidental trauma
 - motor accidents: fetal splenic rupture, case report 318, seat belt injury resulting in fetal death, case reports 320
 - resulting in preterm infants with cerebral lesions, case reports 1292
 - assisted conception *See* In vitro fertilization
 - blood pressure measurements, current practice 241, commentary 239; correspondence 842
 - breech presentation, external cephalic version at term using tocolysis, RCT 8, commentary 1, correspondence 839
 - complicated by hypertensive disorders
 - angiotension II levels 155

- haemodynamic effects of drug therapy 453; correspondence 1187
- histology of placental bed spiral arteries 648; commentary 1195
- historical aspects of toxæmia of pregnancy, review 853
- increased plasma levels of vasoactive intestinal polypeptide 803
- increased platelet turnover with failure of aspirin therapy, case report 218
- PIH associated with elastase-containing neutrophils in placental tissues 929
- platelet angiotensin II binding sites 436
- prevention of pre-eclampsia by intensive hypotensive therapy, RCT 244
- complications
 - AIDS, associated with maternal death, case report 725
 - acute recurrent polyhydramnios, management with indomethacin, case report 583
 - anti-Kell antibodies, frequency 25-year survey 162, correspondence 943
 - anti-Ro (SS-A) antibody, review of current management 751
 - congenital afibrinogenæmia, case report 722
 - congenital coagulopathies, 30-year review of haemorrhagic problems 909
 - Crigler-Nijjar syndrome 1290
 - HELLP syndrome, coagulation studies 42
 - hepatitis B virus infection, prevention and control of perinatal transmission 141
 - hypothyroidism, presenting as hypothermia after pre-eclampsia, case report 218
 - idiopathic thrombocytopenic purpura, case report, correspondence 334, 946
 - in kidney transplant recipient, haemodialysis effects on fetal Doppler velocimetry findings, case report 1172
 - in liver transplant recipient, case report 719
 - lupus nephritis associated with anti-platelet antibodies, case reports 324
 - overlap syndrome, case report 728
 - placental abruption, associated factors, case-control study 448; preceded by abnormal uterine artery FVW 225
 - placenta praevia, early identification, correspondence 499
 - protein C deficiency, unfavourable outcome, case reports 934
 - recurrence of congenital diaphragmatic hernia, case report 110
 - renal failure due to primary renal lymphoma, case report 216
 - rhesus (D) negative women, cost effectiveness of immunoprophylaxis, in India 369; commentary 509 (erratum 1192)
 - spinal cord injuries, management of pregnancy and labour 513
 - Takayasu's arteritis, epidural analgesia for labour 408
 - ureteric obstruction, diagnosis and management 1137
- early diagnosis, hCG excretion, absence of diurnal variation 1180
- ectopic
 - abortion, contraception and smoking risk factors, case-control study, Greece 207
 - aetiological role of *Chlamydia trachomatis* and *Neisseria gonorrhoea* infection in Gabon 1260
 - associated with low serum levels of secretory endometrial protein PP-14, brief report 414
 - audit of management 1267
 - conservative laparoscopic treatment using CO₂-laser, retrospective review 1254
 - diagnostic value of vaginal sonography with serum hCG levels, correspondence 233
 - management, prospective comparison of videopelviscopy with laparotomy 765
 - miscarriage, diagnostic immunohistological demonstration of hPL 463
 - effects on lower urinary tract function following incontinence surgery, case report 1181
 - emergency cervical cerclage, efficacy, 3-year retrospective study 1234
 - fetal growth assessment *See* Fetal, growth assessment
 - gestational age assessment
 - early development crown-rump length, vaginal sonography 460, correspondence 946
 - certain dates are not reliable 108
 - early dating, serum hCG levels and vaginal ultrasound, correspondence 330
 - SGA pregnancies associated with elevated levels of human neutrophil elastase 105
 - management/antenatal care
 - hospital bed rest for twin pregnancy, correspondence 416
 - in developing countries, commentary 345, correspondence 841
 - in women with congenital coagulopathies, 30-year review 909
 - postmature, women's attitudes to conservative management 1102
 - repeated weight gain measurements not recommended 189; correspondence 1055
 - social support, effect on preterm birth, RCT 1001
 - umbilical artery FVWs, predictive value for outcome 378; in high-risk pregnancies RCT 956
 - uteroplacental blood flow studies in second trimester screening for IUGR and pre-eclampsia 871
 - maternal smoking
 - associated with neonatal thyroid enlargement 65
 - stopping smoking: effect of self-help manual, RCT 260, cotinine-intervention, RCT 859; commentary 847
 - maternal weight/fat gain
 - not related to birthweight 254
 - patterns, retrospective study 195, correspondence 1055
 - repeated measurements are not useful 189; correspondence 1055
 - miscarriage *See* Miscarriage
 - nutrition
 - chronic dietary Na restriction, physiological aspects RCT 981
 - fish-oil supplementation, effect on pre-eclampsia, correspondence 499; 737
 - Fe deficiency effect on placental ratio 886
 - Mg intake and status, effect on outcome, Danish population 919
 - metabolic studies
 - fall in plasma osmolality effect on cell hydration 1205
 - serum bile acids in normal pregnancy, longitudinal study 540
 - outcome *See also* Newborn
 - after previous infertility, cohort study 1087
 - effect of Mg nutrition, population study 919
 - previous abortion as affecting, long-term controlled cohort study 1015
 - screening/monitoring
 - serological screening for cytomegalovirus 135
 - uptake of amniocentesis in older women 282
 - urinary tract symptoms correlation with urodynamic findings 1283
- Prostogens *See* Hormone replacement therapy
- Prolactin galactorrhoea and growth hormone excess, case reports 92
- Prostaglandins
 - gemeprost
 - compared with mifepristone for cervical preparation before abortion 1025
 - cervical preparation for abortion 731
 - for midtrimester abortion, associated with uterine rupture, correspondence 416
 - PGE₂
 - and metabolites, production by fetal membranes, in vitro quantitative study 712
 - intravaginal gel for induction of labour 441, correspondence 1314
 - 15-methyl PGF_{2α}, intramyometrial to control atonic postpartum haemorrhage 734

1342 Subject index

- prostaglandin, treatment for postpartum eclampsia and renal failure, case report 400; correspondence 1055
- Protein C deficiency associated with unfavourable pregnancy outcome, case reports 934
- Protozoan infection, congenital toxoplasmosis, diagnosis by cordocentesis, case report 832
- Puerperium
- breast feeding, improved by social support during labour, RCT 756
 - inadequate lactation, response to nasal TRH 880
- Randomized controlled trials (RCT)
- advantages of delivery in an obstetric birth chair 667
 - antenatal social support to prevent preterm birth 1001
 - chronic dietary Na restriction in pregnancy 980
 - cotinine-assisted intervention to reduce smoking in pregnancy 859; commentary 847
 - early amniotomy effect on duration of labour 84; correspondence 1059
 - effects of companionship during labour on progress and breast feeding 756
 - effect of FVW analysis in high risk pregnancies on management 956
 - external cephalic version at term using tocolysis 8; commentary 1, correspondence 839
 - intensive antihypertensive therapy for prevention of pre-eclampsia 244
 - lactational and hormonal response to nasal TRH 880
 - management of third stage using oxytocin, sulprostone and placebo 528
 - mifepristone treatment before abortion, effect on cervical resistance 778
 - sampling efficacy of two cervical spatulas 21; commentary 6
 - self-help manual on stopping smoking in pregnancy 260
- Renin-angiotensin system
- angiotensin II platelet binding sites in normotensive and hypertensive pregnancy 436
 - angiotensin II serum levels in hypertensive pregnancies 155
- Rhesus
- fetal alloimmunization associated with liver dysfunction 287
 - haemolytic disease of the newborn, screening and control in India 369, costs of immunoprophylaxis, commentary 509 (erratum 1192)
- Robertson-Brosens-Dixon hypothesis, evidence for the role of haemochorial placentation in pregnancy success, commentary 1195
- Salpingoscopy *See* Fallopian tubes
- Seat belt injury in pregnancy resulting in fetal death, case reports 320
- Semm cold coagulator, effective destruction of CIN 3, 14 years experience 14
- Skin, presence of oestradiol receptor-related protein, changes during menstrual cycle 1277
- Smoking in pregnancy
- a significant cause of neonatal thyroid enlargement 65
 - risk factor for ectopic pregnancy, case-control study 207
 - stopping smoking
 - cotinine-assisted intervention, RCT 859
 - effect of a self-help manual, RCT 260
 - effects of interventions, commentary 847
- Sodium chronic dietary restriction in pregnancy, physiological aspects, RCT 981
- Spermatozoa, donor insemination, attitudes towards gamete donation 351
- Spinal cord injuries, management of the pregnant woman 513
- Spleen, fetal splenic rupture *in utero* following a road accident, case report 318
- Stamey endoscopic bladder neck suspension, clinical and urodynamic study 1141
- Sterilization tubal, reversal of, role of tuboscopy 326
- Steroids *See also* named compounds
- sex steroids peritoneal fluid levels in mild endometriosis 179
 - Sulprostone in the management of the third stage of labour 528
- Surgery, reducing the risk of infection for obstetricians, commentary 125
- Takayasu's arteritis, epidural analgesia for labour, case report 408
- Thyroid
- enlargement in the newborn associated with maternal smoking 65
 - hypothyroidism presenting as hypothermia in association with pre-eclampsia, case report 221
 - pituitary-thyroid function and fetal circulation, relations 1163
 - thyrotrophin-releasing hormone, nasal administration promoting lactation, RCT 880
- Toxoplasma gondii* congenital toxoplasmosis, diagnosis by cordocentesis, case report 832
- Trichomonas vaginalis* vaginal infection associated with PROM 427
- Trophoblast
- deportation in pre-eclampsia, immunocytological study 973
 - tumours, efficacy of EMA/CO chemotherapy 550
- Tumours *See also* Carcinoma
- gestational trophoblastic, efficacy of EMA/CO chemotherapy 550
 - markers in ovarian cancer, immunoperoxidase localization 73
 - placental chorioangioma associated with theca-lutein cysts, case report 322
- Twin pregnancy
- hospital bed rest, correspondence 416
 - in a woman with idiopathic long QT syndrome, case report 1300
 - maternal serum unconjugated oestriol and hCG levels, implications for screening for Down's syndrome 905
 - perinatal mortality with birthweights under 2500 g, caesarean section as affecting, case-control study 249
 - retention of the second twin after miscarriage of first twin, case reports 1295
- Ultrasound
- Doppler flow velocity waveform studies
 - absent end diastolic associated with normal fetal neurobehavioural development 277
 - blood flow to ovaries after IVF, correspondence 112
 - changes associated with maternal haemodialysis, umbilical artery, case report 1172
 - effect on outcome in high-risk pregnancies 956
 - fetal middle cerebral artery, terminal pattern, case report 937
 - fetal middle cerebral artery and descending thoracic aorta 1163
 - midtrimester uteroplacental, screening study for pre-eclampsia and IUGR 871
 - predictive value for outcome, umbilical artery 378
 - transient improvement after maternal steroid therapy, umbilical artery, case report 492
 - umbilical artery in hypertensive pregnancy, labetalol and hydralazine effects 453; correspondence 1187
 - umbilical artery and maternal angiotensin sensitivity 698
 - uterine artery, abnormal FVW associated with placental abruption, case report 225
 - uteroplacental circulation 1174
 - echocardiography for measurement of fetal cardiac haemodynamics 807
 - guided fetal blood sampling 892
 - transvaginal sonography
 - for CRL in early pregnancy 460; correspondence 946
 - for early pregnancy dating, correspondence 330
 - for endometrial thickness measurement in postmenopause 470
 - hydrotubation for patency testing 1031
 - prognosis of ectopic pregnancy, correspondence 233
 - use in clinical management of vaginal bleeding, case reports 485
- Umbilical cord
- artery flow velocity waveform studies

- and maternal angiotensin sensitivity 698
- in high risk pregnancies effect on outcome, RCT 956
- predictive value for outcome, six-year study 378
- cordocentesis
 - and pregnancy loss in relation to indication 892
 - for diagnosis of congenital toxoplasmosis 832, correspondence 1311
 - for fetal blood gas analysis 820
- vein injection for management of retained placenta 348
- Urinary tract *See also* Bladder
 - detrusor instability, commentary on current management, correspondence 114
 - distal urethral electrical conductance, quick screening test for incontinence 69
 - effects of pregnancy on previous incontinence surgery, case report 1181
 - genuine stress incontinence, diagnostic accuracy of symptoms analysis 815
 - sensory urgency, subjective perception of bladder fullness 1287
 - Stamey endoscopic bladder neck suspension, clinical and urodynamic study 1141
 - stress incontinence, treatment with colpo-needle suspension 1183
 - ureteric obstruction in pregnancy, diagnosis and management 1137
 - uretero-vaginal fistula symptoms controlled with a modified contraceptive diaphragm, case report 101
 - urinary symptoms in early pregnancy, urodynamic assessment 1283
 - voiding in the crouching position, effect on urine flow rate and residual volume 569
- Uterus *See also* Endometrium
 - connective tissue, insufficient remodelling associated with slow progress in labour 1212
 - fibroids, risk of recurrence after myomectomy 385
 - haematometra secondary to HRT, case report 837
 - hysterectomy *See* Hysterectomy
 - hysteroscopic endometrial resection, patient selection 228; correspondence 839, 948
 - rupture in midtrimester abortion induced by gemeprost, correspondence 416
 - utero-cervical angle, effect of cervical traction with a tenaculum 309
 - uteroplacental blood flow velocity studies
 - abnormal pattern associated with placental abruption 225
 - in second trimester, screening for IUGR and pre-eclampsia 871
 - uteroplacental circulation in labour, effects of epidural 1174
 - vaginal hysterectomy combined with prophylactic oophorectomy in 1440 women 662
 - vaginal sonography for management of abnormal bleeding, case reports 485
- Vagina
 - abnormal postmenopausal bleeding, outpatient management with endometrial biopsy 488
 - agenesis
 - free-flap vaginoplasty procedure 184
 - tissue expansion vaginoplasty, procedure and results 564
 - episiotomy repair, use of Histoacryl 476, correspondence 1315
 - epithelial abnormalities in patients with CIN, clinical and pathological features and management 25
 - microflora effect on preterm labour 427
 - transvaginal sonography
 - for CRL measurement 460, correspondence 946
 - for ectopic pregnancy, correspondence 233
 - for endometrial thickness in postmenopause 470
 - for management of abnormal bleeding 485
 - hydrotubation for patency testing 1031
 - uretero-vaginal fistula, symptoms relieved with a contraceptive diaphragm, case report 101
 - vault prolapse, surgical management 1150
 - vaginal hysterectomy combined with prophylactic oophorectomy in 1440 women 662
- Verapamil (Ca antagonist), effect on respiratory function in severe pre-eclampsia 964
- Virus infections
 - congenital and maternal cytomegalovirus infections in a London population 135
 - hepatitis B, perinatal transmission, prevention and control 141
 - human immunodeficiency virus (HIV)
 - AIDS, cause of maternal death, case report 725
 - clinical presentation in a genitourinary medicine clinic 103, correspondence 612
 - HIV-type 1 seroconversion in pregnancy, effect on perinatal transmission 940
 - human papilloma virus (HPV) cervical infection, serial histological changes correlated with HPV genome detection 1042
 - reducing the risk of infection for obstetricians, commentary 125
- Vitamin B therapy for premenstrual syndrome, correspondence 329
- Vulva
 - Darrier's disease, correspondence 112
 - reconstruction by free tissue transfer, case report 98, 613
 - scarring, cicatricial pemphigoid diagnosed from ocular features, case reports 482
 - vestibulitis syndrome, clinicopathological study 703
 - vulvodynia and selective IgA deficiency, case reports 592
- Water, cellular overhydration associated with fall in plasma osmolality in normal pregnancy 1205
- Zoladex *See* Goserelin

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CONTENTS

Vol 98 No 1 January 1991

- 1 Commentaries
External cephalic version at term: how high are the stakes?
G. J. Hofmeyr
The treatment of CIN: do we need lasers?
J. A. Giles & A. Gafar
What constitutes an adequate cervical smear?
J. E. Macgregor
- 8 External cephalic version at term. A randomized controlled trial using tocolysis
K. Mahomed, R. Seeras & R. Coulson
- 14 Effective destruction of cervical intraepithelial neoplasia (CIN) 3 at 100°C using the Semm cold coagulator: 14 years experience
H. K. Gordon & I. D. Duncan
- 21 A randomized control trial of two cervical spatulas
C. J. B. Woodman, M. Yates, D. R. Williams, K. Ward, J. Jordan & D. Luesley
- 25 Vaginal epithelial abnormalities in patients with CIN: clinical and pathological features and management
N. J. Nwabine & J. M. Monaghan
- 30 Treatment of anovulation due to polycystic ovarian syndrome by laparoscopic ovarian electrocautery
G. Kovacs, H. Buckler, M. Bangah, K. Outch, H. Burger, D. Healy, G. Baker & S. Phillips
- 36 Fetal monitoring with pulse oximetry
N. Johnson, V. A. Johnson, J. Fisher, B. Jobbings, J. Bannister & R. J. Lulford
- 42 Coagulation studies in the syndrome of haemolysis, elevated liver enzymes and low platelets
K. De Boer, H. R. Buller, J. W. Ten Cate & P. E. Treffers
- 48 Fetal crown-rump length values in the first trimester based upon ovulation timing using the luteinizing hormone surge
J. Evans
- 52 Ratio of immunochemically determined amniotic fluid acetylcholinesterase to butyrylcholinesterase in the differential diagnosis of fetal abnormalities
A. G. Rasmussen Loft, V. Mortensen, J. Hangaard & B. Nørgaard-Pedersen
- 57 Babies born before arrival at hospital
P. S. Bhoopalam & M. Watkinson
- 65 Smoking during pregnancy: a significant cause of neonatal thyroid enlargement
J. P. Chanoine, V. Toppet, P. Bourdoux, M. Spehl & F. Delange
- 69 Distal urethral electrical conductance (DUEC)—a preliminary assessment of its role as a quick screening test for incontinent women
S. M. Creighton, S. Plevnik & S. L. Stanton
- 73 The immunoperoxidase localization of tumour markers in ovarian cancer: the value of CEA, EMA, cytokeratin and DD9
R. H. Hammond, T. D. Bates, D. G. Clarke, A. G. Grant, A. M. R. Haines, D. L. S. Eustace & E. Heyderman
- 84 A randomized controlled trial of early amniotomy
W. D. Fraser, R. Sauve, I. J. Parboosingh, T. Fung, R. Sokol & D. Presaud
- 92 Growth hormone excesses and galactorrhoea without acromegalic features. Case reports
R. Pestell, A. Herington, J. Best, M. Boolell, P. McKelvie, R. Arnott & F. Alford
- 98 Vulval reconstruction by free tissue transfer. Case report
S. Srivastava & R. Maxwell
- 101 A modified contraceptive diaphragm for relief of uretero-vaginal fistula. Case report
P. J. Banfield, G. Scott & H. R. M. Roberts
- 103 Short communications
The clinical presentation of women with human immunodeficiency virus infection
P. D. Kell, S. E. Barton, D. A. Hawkins, R. Marwood & L. C. Howard
Neutrophil activation in small for gestational age pregnancies
T. A. Johnston, I. A. Greer, J. Dawes & A. A. Calder
Quantitation of hormone replacement induced withdrawal bleeds
M. C. P. Rees & D. H. Barlow

Certain dates may not provide a reliable estimate of gestational age

R. T. Geirsson & R. M. Busby-Earle

Late recurrence of a congenital diaphragmatic hernia. Case report

B. M. Stephenson & J. D. Stamatakis

112 Correspondence

117 Book reviews

Vol 98 No 2 February 1991

121 Commentaries

Medical Education

D. W. Purdie

Reducing the risk of infection for obstetricians

J. R. Smith & V. S. Kuchen

127 Undergraduate obstetrics and gynaecology in the United Kingdom and the Republic of Ireland, 1989

J. S. G. Biggs, R. M. Harden & P. Howie

135 Congenital and maternal cytomegalovirus infections in a London population

P. D. Griffiths, C. Baboonian, D. Rutter & C. Peckham

141 Perinatal transmission of hepatitis B virus infection: a recommended strategy for prevention and control. A review

S. Ramia & M. Arif

147 Early postoperative mortality following hysterectomy. A Danish population based study, 1977–1981

A. Loft, T. F. Andersen, H. Brønnum-Hansen, C. Roepstorff & M. Madsen

155 Angiotensin II levels in hypertensive and normotensive pregnancies

M. Hanssens, M. J. N. C. Keirse, B. Spitz & F. A. van Assche

162 Anti-Kell in pregnancy

H. M. Leggat, J. M. Gibson, S. L. Barron & M. M. Reid

166 Life events and low birthweight—analysis by infants preterm and small for gestational age

T. Mutale, F. Creed, M. Maresh & L. Hunt

173 Comparison of the T/QRS ratio of the fetal electrocardiogram and the fetal heart rate during labour and the relation of these variables to condition at delivery

S. Newbold, T. Wheeler & F. Clewlow

179 Peritoneal fluid volume and sex steroids in the pre-ovulatory period in mild endometriosis

T. A. Mahmood & A. Templeton

184 The free-flap vaginoplasty; a new surgical procedure for the treatment of vaginal agenesis

N. Johnson, R. J. Lilford & A. Batchelor

189 Repeated measurement of maternal weight during pregnancy. Is this a useful practice?

M. G. Dawes & J. G. Grudzinskas

195 Patterns of maternal weight gain in pregnancy

M. G. Dawes & J. G. Grudzinskas

202 Atrial natriuretic peptide and atrial size during normal pregnancy

E. A. P. Steegers, H. P. J. M. van Lakwijk, J. H. Fast, A. W. H. J. Godschalx, H. W. Jongsma, T. K. A. B. Eskes, E. M. Symonds & P. R. Hein

207 Induced abortions, contraceptive practices, and tobacco smoking as risk factors for ectopic pregnancy in Athens, Greece

A. Kalandidi, M. Doulgerakis, A. Tzonou, C.-C. Hsieh, D. Aravandinos & D. Trichopoulos

214 The vanishing bowel. Case report of bowel atresia following gastroschisis

N. Johnson, R. J. Lilford, H. Irving, D. Crabbe & R. Cartmill

216 Renal failure in pregnancy due to primary renal lymphoma. Case report

O. Sheil, C. W. G. Redman & C. Pugh

218 Increased platelet turnover in a patient with previous recurrent pre-eclampsia and failure of aspirin therapy. Case report

Y. Ahmed, M. H. F. Sullivan & M. G. Elder

221 Hypothyroidism presenting as hypothermia following pre-eclampsia at 23 weeks gestation. Case report and review of the literature

L. Mizgala, T. T. Lao & M. E. Hannah

225 Placental abruption preceded by abnormal flow velocity waveforms in the uterine arteries. Case report

H. Oosterhof & J. G. Aarnoudse

- 226 Errata
- 227 Short communications
 - Diplopia after labour. Case report
 - P. Nucci, E. Conti, S. Bianchi, L. Pierro & R. Brancato*
 - Patient selection for hysteroscopic endometrial resection
 - A. J. Rutherford, M. R. Glass & M. Wells*
- 231 Correspondence
- 234 Book reviews

Vol 98 No 3 March 1991

- 237 Commentaries
 - The future obstetrician/gynaecologist
 - S. Bewley*
 - Blood pressure measurement in pregnancy
 - M. de Swiet*
- 241 Conflicting views on the measurement of blood pressure in pregnancy
 - I. J. Perry, L. S. Wilkinson, R. A. Shinton & D. G. Beevers*
- 244 The prevention of the maternal manifestations of pre-eclampsia by intensive antihypertensive treatment
 - S. Blake & D. MacDonald*
- 249 A case-control study of the effects of birth by caesarean section on intrapartum and neonatal mortality among twins weighing 1500–2499 g
 - H. Rydhstrom & I. Ingemarsson*
- 254 Women who gain more fat during pregnancy may not have bigger babies: implications for recommended weight gain during pregnancy
 - M. Lawrence, F. M. McKillop & J. V. G. A. Durnin*
- 260 Stopping smoking in pregnancy: effect of a self-help manual in controlled trial
 - A. I. M. Hjalmarsen, L. Hahn & B. Svanberg*
- 265 Scar rupture in labour after previous lower uterine segment caesarean section: the role of uterine activity measurement
 - S. Beckley, H. Gee & J. R. Newton*
- 270 Lactation inhibition by the dopamine agonist CV 205–502
 - P. F. M. van der Heijden, J. A. M. Kremer, J. Brownell & R. Rolland*
- 277 Continuation of normal neurobehavioural development in fetuses with absent umbilical arterial end diastolic velocities
 - M. Pillai & D. James*
- 282 Perceived risk not actual risk predicts uptake of amniocentesis
 - T. M. Marteau, J. Kidd, R. Cook, S. Michie, M. Johnston, J. Slack & R. W. Shaw*
- 287 Fetal liver dysfunction in Rh alloimmunization
 - U. Nicolini, P. Nicolaidis, Y. Tannirandorn, N. M. Fisk, H. Nasrat & C. H. Rodeck*
- 294 Oestrogen and androgen states in oligo-amenorrhoeic women with polycystic ovaries
 - R. Fox, E. Corrigan, P. G. Thomas & M. G. R. Hull*
- 300 Polycystic ovaries: do these represent a specific endocrinopathy?
 - A. Abdel Gadir, M. S. Khatim, R. S. Mowafi, H. M. I. Alnaser, H. G. N. Alzaid & R. W. Shaw*
- 306 The miscarriage clinic. an audit of the first year
 - M. J. Turner, G. M. Flannelly, M. Wingfield, M. J. Rasmussen, R. Ryan, S. Cullen, R. Maguire & J. M. Stronge*
- 309 Effect of cervical traction with a tenaculum on the uterocervical angle
 - N. Johnson & D. R. Bromham*
- 313 The use of cervicography in a primary screening service
 - A. Szarewski, J. Cuzick, R. Edwards, B. Butler & A. Singer*
- 318 Splenic rupture in utero following a road traffic accident. Case report
 - J. N. Siddall-Allum, J. H. Hughes, S. Kaler & P. W. Reginald*
- 320 Seat belt injury in pregnancy resulting in fetal death. A need for education? Case reports
 - M. Griffiths, G. Hullman & M. McD. Usherwood*
- 322 Theca-lutein ovarian cysts associated with placental chorioangioma. Case report
 - P. A. King, A. Lopes, M. H. Y. Tang, S. K. Lam & H. K. Ma*

- 324 Anti-platelet antibodies: a prognostic marker in pregnancies associated with lupus nephritis. Case reports
M. J. McCormack, D. Adu, J. Weaver, J. Michael & J. Kelly
- 326 Short communications
 Tuboscopy in a previously sterilized patient
S. D. Maguiness & O. Djahanbakhch
 Role of menstrual blood loss measurements in management of complaints of excessive menstrual bleeding
M. C. P. Rees
- 329 Correspondence
- 337 Book reviews

Vol 98 No 4 April 1991

- 343 Commentaries
 Gamete donation and anonymity
A. Templeton
 Obstetric mortality and its causes in developing countries
T. Barns
 Management of retained placenta by umbilical vein injection
G. Carroli
- 351 Attitudes towards gamete donation among couples undergoing in vitro fertilization
T. Oskarsson, E. S. Dmitry, M. S. Mills, J. Hunt & R. M. L. Winston
- 357 A multi-centre collaborative study into the treatment of menorrhagia by Nd-YAG laser ablation of the endometrium
R. Garry, J. Erian & S. A. Grockmal
- 363 Phospholipase activity in the endometrium of women with normal menstrual blood loss and women with proven ovulatory menorrhagia
R. C. Bonney, J. M. Higham, H. Watson, J. S. Beesley, R. W. Shaw & S. Franks
- 369 Controlling Rh haemolytic disease of the newborn in India
K. S. Joseph
- 378 Fetal umbilical artery velocity waveforms and subsequent neonatal outcome
B. J. Trudinger, C. M. Cook, W. B. Giles, S. Ng, E. Fong, A. Connelly & W. Wilcox
- 385 Risk of recurrence after myomectomy
G. B. Candiani, L. Fedele, F. Parazzini & L. Villa
- 390 Obstetric accidents: the patient's perspective
C. A. Vincent, T. Martin & M. Ernis
- 396 Psychiatric morbidity and acceptability following medical and surgical methods of induced abortion
D. R. Urquhart & A. A. Templeton
- 400 Post partum eclampsia and acute renal failure; treatment with prostacyclin. Case report
J. G. Fox, N. P. Sutcliffe, J. J. Walker & M. E. M. Allison
- 403 Spontaneous variation in fetal pleural effusions. Case report
M. Parker & D. James
- 406 Renal endometriosis treated with a gonadotrophin releasing hormone agonist. Case report
D. Hellberg, B. Fors & C. Bergqvist
- 408 Epidural analgesia for labour in Takayasu's arteritis. Case report
S. L. Crofts & E. Wilson
- 410 Acromegaloïd bone changes in severe polycystic ovarian disease: an effect of hyperinsulinaemia? Case report
R. Fox, P. G. Wardle, L. Clarke & M. G. R. Hull
- 413 Short communications
 Intrauterine infection and miscarriage following trans-abdominal chorionic villus sampling. Case report
A. Garden, M. Johnston & N. Davis
 Serum level of secretory endometrial protein PP-14 in intact ectopic pregnancy
J. F. Pedersen, S. Sørensen & S. Kuge
- 415 Correspondence
- 418 Book reviews

Vol 98 No 5 May 1991

- 423 Commentary
Litigation in obstetrics and gynaecology
R. V. Clements
- 427 Vaginal infection and preterm labour
H. M. McDonald, J. A. O'Loughlin, P. Jolley, R. Vigneswaran & P. J. McDonald
- 436 Platelet angiotensin II binding sites in normotensive and hypertensive women
P. N. Baker, F. Broughton Pipkin & E. M. Symonds
- 441 Intrauterine pressures in labours induced by amniotomy and oxytocin or vaginal prostaglandin gel compared with spontaneous labour
R. F. Lamont, S. Neave, A. C. Baker & P. J. Steer
- 448 Placental abruption. A case-control investigation
G. Eriksen, M. Wohler, V. Ersbak, L. Hvidman, M. Hedegaard & K. Skajaa
- 453 Maternal and fetal haemodynamics in hypertensive pregnancies during maternal treatment with intravenous hydralazine or labetalol
A. Harper & G. A. Murnaghan
- 460 The crown-rump length in early human pregnancy: a reappraisal
R. Schats, H. C. Van Os, C. A. M. Jansen & J. W. Wladimiroff
- 463 Immunohistological demonstrations of intermediate trophoblast in the diagnosis of uterine versus ectopic pregnancy: a retrospective survey and results of a prospective trial
F. B. Sørensen, N. Marcussen, H. O. Daugaard, J. D. Kristansen, J. Møller & H. J. Ingerslev
- 470 The role of vaginal scan in measurement of endometrial thickness in postmenopausal women
M. N. Nasri, J. H. Shepherd, M. E. Setchell, D. G. Lowe & T. Chard
- 476 The use of Histoacryl for episiotomy repair
A. Adoni & E. Anteby
- 479 The tap test—a rapid bedside indicator of fetal lung maturity
F. Guidozi & L. Gobetz
- 482 Cicatricial pemphigoid diagnosed from ocular features in recurrent severe vulval scarring. Two case reports
P. Frith, M. Charnock & F. Wojnarowska
- 485 Transvaginal ultrasound. A reliable basis for clinical management? Case reports
M. N. Nasri, J. H. Shepherd, M. E. Setchell, D. G. Lowe & T. Chard
- 487 Short communications
Maternal impressions of forceps or the Silc-cup
J. Pusey, C. Hodge P. Wilkinson & R. Johanson
An out-patient approach to the management of post-menopausal bleeding
A. G. Shaker, M. Anderson, H. C. Kuchener & I. D. Miller
Lesion size and histology of atypical cervical transformation zone
M. I. Shafi, C. B. Finn, D. M. Luesley, J. A. Jordan & J. Dunn
Transient improvement of umbilical arterial waveform after maternal steroid administration
A. Leung, E. Neale & M. Rogers
First trimester CA 125 and Down's syndrome
J. M. M. van Luth, A. Mantingh, J. R. Beekhuis, H. W. A. de Bruijn & A. S. P. M. Breed
- 495 Blair Bell Research Society
- 499 Correspondence
- 504 Book reviews
- 508 Erratum

Vol 98 No 6 June 1991

- 509 Commentary
Immunoprophylaxis for rhesus disease—expensive but worth it?
M. Selinger

- 513 Management of the pregnant woman with spinal cord injuries
S. J. Hughes, D. J. Short, M. McD. Usherwood & H. Tebbutt
- 519 How does the mode of delivery affect the cost of maternity care?
L. Clark, M. Mugford & C. Paterson
- 524 Head circumference/abdominal circumference ratio, ponderal index and fetal malnutrition. Should head circumference/abdominal circumference ratio be abandoned?
N. V. Colley, J. M. Tremble, G. L. Henson & T. J. Cole
- 528 A randomized comparison of oxytocin, sulprostone and placebo in the management of the third stage of labour
R. P. Poeschmann, W. H. Doesburg & T. K. A. B. Eskes
- 531 How obstetricians manage the problem of preterm delivery with special reference to the preterm breech
Z. J. Penn & P. J. Steer
- 535 Trends in multiple births in Italy: 1955–1983
F. Parazzini, L. Tozzi, G. Mezzanotte, L. Bocciolone, C. La Vecchia, L. Fedele & G. Benzi
- 540 Serum bile acids in normal pregnancy
J. Carter
- 544 The use of the GnRH analogue buserelin for IVF—does it improve fertility?
K. Shelton, S. Fishel, P. Jackson, J. Webster, B. Faratian & J. Johnson
- 550 Results with the EMA/CO (etoposide, methotrexate, actinomycin D, cyclophosphamide, vincristine) regimen in high risk gestational trophoblastic tumours, 1979 to 1989
E. S. Newlands, K. D. Bagshawe, R. H. J. Begent, G. J. S. Rustin & L. Holden
- 558 Menstrual symptoms in women with pelvic endometriosis
T. A. Mahmood, A. A. Templeton, L. Thomson & C. Fraser
- 564 Experience with tissue expansion vaginoplasty
N. Johnson, A. Batchelor & R. J. Lilford
- 569 Crouching over the toilet seat: prevalence among British gynaecological outpatients and its effect upon micturition
K. H. Moore, D. H. Richmond, J. R. Sutherst, A. H. Imrie & J. L. Hutton
- 573 Oocyte and follicular fluid characteristics in women with mild endometriosis
T. A. Mahmood, K. Arumugam & A. A. Templeton
- 578 Immunoreactive endometritis
H. Skensved, A. Hansen & M. Vetter
- 583 Acute recurrent polyhydramnios—management with indomethacin
H. Z. Malas & J. D. Hamlett
- 588 Is large loop excision of the transformation zone (LLETZ) more accurate than colposcopically directed punch biopsy in the diagnosis of cervical intraepithelial neoplasia?
D. T. Howe & A. C. Vincenti
- 592 Vulvodynia and selective IgA deficiency. Case reports
F. Scrimin, C. Volpe, G. Tracanzan, F. G. Toffoletti & F. Barciulli
- 594 Placenta accreta and myotonic dystrophy. Two case reports
R. M. Freeman
- 596 Ovarian necrotizing vasculitis causing major intra-abdominal haemorrhage after IVF. Case report and literature review
M. Ilbery, B. Lyons & V. Sundaresan
- 600 Imaging of pulmonary endometriosis by immunoscintigraphy. Case report
S. Kennedy, S. Mojumuyi, N. Soper, J. Spencer, B. Shepstone & D. Barlow
- 602 Raised serum CA 125 preceding the diagnosis of carcinoma of the fallopian tube: two case reports
A. Prys Davies, A. Fish, R. Woolas & D. Oram
- 604 Short communication
Pre-eclampsia and anti-phospholipid antibody
P. V. Taylor, S. M. Skerrow & C. W. G. Redman
- 607 Correspondence
- 614 Book reviews

- Quality of the perinatal autopsy
J. S. Wigglesworth
 Management of tubal infertility in the 1990s
H. Reuss
- 624 West Midlands perinatal mortality survey, 1987. An audit of 300 perinatal autopsies
D. I. Rushton
- 628 An analysis of factors influencing the outcome of 232 consecutive tubal microsurgery cases
V. Singhal, T. C. Li & D. Cooke
- 637 Microsurgical salpingostomy is not an obsolete procedure
R. M. L. Winston & R. A. Margara
- 643 Is GIFT (gamete intrafallopian transfer) the best treatment for unexplained infertility?
A. P. Murdoch, M. Harris, M. Mahroo, M. Williams & W. Dunlop
- 648 Placental bed spiral arteries in the hypertensive disorders of pregnancy
R. Pijnenborg, J. Anthony, D. A. Davey, A. Rees, A. Tiltman, L. Vercruysse & A. Van Assche
- 656 The variation of endometrial response to a standard hormone replacement therapy in women with premature ovarian failure. An ultrasonographic and histological study
T. C. Li, P. Dockery, S. S. Ramsewak, L. Klentzers, E. A. Lenton & I. D. Cooke
- 662 The place of oophorectomy at vaginal hysterectomy
S. S. Sheth
- 667 Delivery in an obstetric birth chair: a randomized controlled trial
P. Crowley, D. Elbourne, H. Ashurst, J. Garcia, D. Murphy & N. Duignan
- 675 Partial placenta membranacea
B. S. Wilkins, G. Batcup & P. S. Vinall
- 680 Autoreactivity in women with endometriosis
P. V. Taylor, M. D. Maloney, J. M. Campbell, S. M. Skerrow, M. M. C. Nip, R. Parmar & G. Tate
- 685 Maternal plasma corticotrophin-releasing hormone—elevated in preterm labour but unaffected by indomethacin or nylidrin
T. Kurki, T. Laatikainen, K. Salmunen-Lappalainen & O. Ylikorkala
- 692 Prediction of lethal pulmonary hypoplasia and chorioamnionitis by assessment of fetal breathing
A. Ohlsson, K. Fong, M. Hannah, Z. Heyman, R. Gonen, T. Rose & R. Baboolal
- 698 Maternal angiotensin sensitivity and fetal Doppler umbilical artery flow waveforms
C. M. Cook & B. J. Trudinger
- 703 Vulvar vestibulitis syndrome: a clinico-pathological study
C. B. Furlonge, R. N. Thun, B. E. Evans & P. H. McKee
- 707 A comparative study of ethamsylate and mefenamic acid in dysfunctional uterine bleeding
G. Chamberlain, R. Freeman, F. Price, A. Kennedy, D. Green & L. Eve
- 712 Quantitative production of prostaglandin E_2 and its metabolites by human fetal membranes
H. Khan, M. H. F. Sullivan, R. Helmig, C. K. Roseblade, N. Uldbjerg & M. G. Elder
- 716 The role of postnatal x-ray pelvimetry after caesarean section in the management of subsequent delivery
S. Krishnamurthy, F. Fairlie, A. D. Cameron, J. J. Walker & J. R. Mackenzie
- 719 Pregnancy after orthotopic liver transplantation. Case report
N. C. W. Hill, N. H. Morris, R. W. Shaw, S. Mathur, K. Rolles & A. K. Burroughs
- 722 Congenital afibrinogenaemia and successful pregnancy outcome. Case report
A. K. Trehan & I. L. C. Fergusson
- 725 A maternal death caused by AIDS. Case report
P. D. Kell, S. E. Barton, D. E. Smith, M. Nelson, R. P. Marwood & B. Gazzard
- 728 Overlap syndrome and its implications in pregnancy. Case report
K. S. Oláh & C. W. G. Redman
- 731 Short communications
 Cervical preparation with gemeprost for dilatation and evacuation
J. A. D. Spencer, P. Nicolaidis, A. Lee, U. Nicolini & C. H. Rodeck
 Early endometrial carcinoma: an incidental finding after endometrial resection. Case report
N. A. Dwyer & G. M. Stirrat
 Use of intra myometrial 15-methyl prostaglandin $F_{2\alpha}$ to control atonic postpartum haemorrhage following vaginal delivery and failure of conventional therapy
A. Bigrigg, D. Chui, S. Chussell & M. D. Read
- 737 Correspondence
- 744 Book reviews

Vol 98 No 8 August 1991

- 749 Commentary
Progestogens, lipid metabolism and hormone replacement therapy
D. Crook & J. C. Stevenson
- 751 Fetal heart block associated with maternal anti-Ro (SS-A) antibody—current management.
A review
K. S. Oláh & H. Gee
- 756 Companionship to modify the clinical birth environment: effects on progress and perceptions of labour, and breastfeeding
G. J. Hofmeyr, V. C. Nikodem, W.-L. Wolman, B. E. Chalmers & T. Kramer
- 765 Prospective comparison of videopelviscopy with laparotomy for ectopic pregnancy
R. Baumann, A. L. Magos & A. Turnbull
- 772 Audit of workload in gynaecology: analysis of time trends from linked statistics
J. A. Ferguson, M. J. Goldacre, J. Henderson & M. D. G. Gillmer
- 778 Pretreatment of the primigravid uterine cervix with mifepristone 30 h prior to termination of pregnancy: a double blind study
M. Cohn & P. Stewart
- 783 Follicular development in spontaneous and stimulated cycles in women with minimal-mild endometriosis
T. A. Mahmood, I. E. Messinis & A. Templeton
- 789 Outcomes of referrals to gynaecology outpatient clinics for menstrual problems: an audit of general practice records
A. Coulter, J. Bradlow, M. Agass, C. Martin-Bates & A. Tulloch
- 797 'Nuns, virgins, and spinsters.' Rigoni-Stern and cervical cancer revisited
M. Griffiths
- 803 Increased plasma levels of vasoactive intestinal polypeptide in pre-eclampsia
N. Holst, P. Øian, B. Aune, T. G. Jenssen & P. G. Burhol
- 807 Reproducibility of ultrasonic measurement of fetal cardiac haemodynamics
A. R. Beeby, W. Dunlop, A. Heads & S. Hunter
- 815 Symptoms analysis for the diagnosis of genuine stress incontinence
E. Versi, L. Cardozo, D. Anand & D. Cooper
- 820 Relation of fetal blood gases and data from computer-assisted analysis of fetal heart rate patterns in small for gestation fetuses
L. S. M. Ribbert, R. J. M. Snijders, K. H. Nicolaides & G. H. A. Visser
- 824 Computerization of a colposcopy clinic
W. P. Soutter
- 829 Direct antenatal fetal electrocardiographic waveform analysis
S. Arulkumaran, U. Nicolini, N. M. Fisk, Y. Tannirandorn, K. G. Rosen & C. H. Rodeck
- 832 Difficulties in the diagnosis of congenital toxoplasmosis by cordocentesis. Case report
R. E. Holliman, J. D. Johnson, G. Constantine, J. G. Bissenden, K. Nicolaides & D. Savva
- 835 Short communication
CA 125 and preterm prelabour rupture of the membranes
P. J. Danielian
- 837 Haematometra secondary to hormone replacement therapy. Case report
N. Morris, N. Amso & P. Chalk
- 839 Correspondence
- 844 Book reviews

Vol 98 No 9 September 1991

- 847 Commentaries
Stopping smoking—again
J. Lumley
First trimester prenatal diagnosis: chorion villus sampling or amniocentesis?
J. P. Neilson & C. M. Gosden
- 853 Some historical aspects of toxæmia of pregnancy. A review
I. Loudon

- 859 Cotinine-assisted intervention in pregnancy to reduce smoking and low birthweight delivery
J. E. Haddow, G. J. Knight, E. M. Kloza, G. E. Palomaki & N. J. Wald
- 866 Early amniocentesis: alphafetoprotein levels in amniotic fluid, extraembryonic coelomic fluid and maternal serum between 8 and 13 weeks
N. C. Wathen, P. L. Cass, D. J. Campbell, M. J. Kutau & T. Chard
- 871 Doppler investigation of uteroplacental blood flow resistance in the second trimester: a screening study for pre-eclampsia and intrauterine growth retardation
S. Bewley, D. Cooper & S. Campbell
- 880 Thyrotrophin-releasing hormone—a lactation-promoting agent?
F. Peters, J. Schulze-Tollert & W. Schuth
- 886 The effect of maternal anaemia and iron deficiency on the ratio of fetal weight to placental weight
K. M. Godfrey, C. W. G. Redman, D. J. P. Barker & C. Osmond
- 892 Fetal blood sampling and pregnancy loss in relation to indication
D. J. Maxwell, P. Johnson, P. Hurley, K. Neales, L. Allan & P. Knott
- 898 Mode of delivery and neonatal death in 17 587 infants presenting by the breech
J. L. Kiely
- 905 Maternal serum unconjugated oestriol and human chorionic gonadotrophin levels in twin pregnancies: implications for screening for Down's syndrome
N. Wald, H. Cuckle, T. Wu & L. George
- 909 Haemorrhagic problems in obstetrics and gynaecology in patients with congenital coagulopathies
I. A. Greer, G. D. O. Lowe, J. J. Walker & C. D. Forbes
- 919 Magnesium intake and status and pregnancy outcome in a Danish population
K. Skajaa, I. Dørup & B.-M. Sandstrom
- 929 Immunocytochemical localization of neutrophil elastase in term placenta decidua and myometrium in pregnancy-induced hypertension
B. H. Butterworth, I. A. Greer, W. A. Liston, N. G. Haddad & T. A. Johnston
- 934 Unfavourable pregnancy outcome associated with congenital protein C deficiency. Case reports
D. Bertault, L. Mandelbrot, C. Tchobroutsky & Y. Sultan
- 937 Fetal middle cerebral artery flow velocity waveforms—a terminal pattern. Case report
R. Chandran, V. Serra Serra, S. M. Sellers & C. W. G. Redman
- 939 Short communications
The endometrial status of women on long-term continuous combined hormone replacement therapy
R. J. S. Hawthorn, K. Spowart, D. Walsh & D. McKay Hart
Human immunodeficiency virus type 1 (HIV-1) seroconversion during pregnancy does not increase the risk of perinatal transmission
P.-A. Tovo, E. Palomba, C. Gabiano, L. Gallu & M. de Martino
- 943 Correspondence
- 949 Book reviews

Vol 98 No 10 October 1991

- 953 Commentary
What is birth asphyxia?
J. Hull & K. Dodd
- 956 Doppler flow velocity waveform analysis in high risk pregnancies: a randomized controlled trial
J. P. Newnham, M. R.-A. O'Dea, K. P. Reid & D. A. Diepeveen
- 964 Respiratory function in severe gestational proteinuric hypertension: the effects of rapid volume expansion and subsequent vasodilatation with verapamil
M. A. Belfort, J. Anthony & B. Kirshon
- 973 Trophoblast deportation in pre-eclamptic pregnancy
S. Chua, T. Wilkins, I. Sargent & C. Redman
- 980 (Patho)physiological implications of chronic dietary sodium restriction during pregnancy; a longitudinal prospective randomized study
E. A. P. Steegers, H. P. J. M. van Lakwijk, H. W. Jongsma, J. H. Fast, T. De Boo, T. K. A. B. Eskes & P. R. Hein
- 988 Bilateral oophorectomy and hysterectomy in the treatment of intractable pelvic pain associated with pelvic congestion
R. W. Beard, R. G. Kennedy, K. F. Gangar, R. W. Stones, V. Rogers, P. W. Reginald & M. Anderson

- 993 Cancer of the cervix in women under 40 years of age, a regional survey, 1975–1984
K. R. Peel, G. G. Khoury, C. A. F. Joslin, P. J. O'Donovan, H. Mgaya, G. Keates, C. Head & D. J. Thorogood
- 1001 Randomized controlled trial of antenatal social support to prevent preterm birth
R. L. Bryce, F. J. Stanley & J. B. Garner
- 1009 Pre-eclampsia and offspring's blood pressure, cognitive ability and physical development at 17-years-of-age
D. S. Seidman, A. Laor, R. Gale, D. K. Stevenson, S. Mashach & Y. L. Danon
- 1015 The effect of induced abortion on subsequent pregnancy outcome
P. I. Frank, R. McNamee, P. C. Hannaford, C. R. Kay & S. Hirsch
- 1025 Pre-operative cervical preparation before first trimester vacuum aspiration: a randomized controlled comparison between gemeprost and mifepristone (RU 486)
R. C. Henshaw & A. A. Templeton
- 1031 A clinical comparison of sonographic hydrotubation and hysterosalpingography
F. F. Mitri, A. D. Andronikou, S. Perpunyal, G. J. Hofmeyr & E. W. W. Sonnendecker
- 1037 A new treatment for endometrial cancer with gonadotrophin releasing-hormone analogue
G. J. Gallagher, R. T. D. Oliver, D. H. Oram, C. G. Fowler, P. R. Blake, B. S. Mantell, M. L. Slevin & H. F. Hope-Stone
- 1042 Prospective serial study of viral change in the cervix and correlation with human papillomavirus genome status
H. C. Kitchener, L. Neilson, R. A. Burnett, L. Young & J. C. M. Macnab
- 1049 A review of 80 endometrial resections for menorrhagia
R. J. D. Pyper & A. D. Haeri
- 1055 Correspondence
- 1061 Book reviews

Vol 98 No 11 November 1991

- 1065 Commentaries
Audit in obstetrics
S. L. Barron
The flying squad
G. Chamberlain & J. M. Pearce
Criteria for standards of management of women with an abnormal smear
W. P. Soutter
- 1073 Evaluating the quality of the maternity services—a discussion paper
C. M. Paterson, J. C. Chapple, R. W. Beard, M. Joffe, P. J. Steer & C. S. W. Wright
- 1079 Is genetic susceptibility to pre-eclampsia conferred by homozygosity for the same single recessive gene in mother and fetus?
W. A. Liston & D. C. Kilpatrick
- 1087 The obstetric and neonatal outcome of pregnancy in women with a previous history of infertility: a prospective study
T. C. Li, I. MacLeod, V. Singhal & S. L. B. Duncan
- 1093 The prevalence, aetiology and clinical significance of pseudo-sinusoidal fetal heart rate patterns in labour
K. W. Murphy, V. Russell, A. Collins & P. Johnson
- 1102 The management of prolonged pregnancy—an analysis of women's attitudes before and after term
L. J. Roberts & K. R. Young
- 1107 Gamete intrafallopian transfer (GIFT) compared with intrauterine insemination in the treatment of unexplained infertility
A. P. Murdoch, M. Harris, M. Mahroo, M. Williams & W. Dunlop
- 1112 United Kingdom Colposcopy Survey, British Society for Colposcopy and Cervical Pathology
H. C. Kitchener
- 1117 A multicentre study of coagulation and haemostatic variables during oral contraception: variations with four formulations
WHO Task Force on Oral Contraceptives
- 1129 Self-reported long-term outcomes of hysterectomy
M. J. Schofield, A. Bennett, S. Redman, W. A. W. Walters & R. W. Sanson-Fisher

- 1137 Ureteric obstruction in pregnancy—diagnosis and management
S. D. Eckford & J. C. Gingell
- 1141 The Stamey endoscopic bladder neck suspension: a clinical and urodynamic investigation, including actuarial follow-up over four years
P. Hilton & C. J. Mayne
- 1150 The surgical management of vaginal vault prolapse
S. M. Creighton & S. L. Stanton
- 1155 The combination of a depot gonadotrophin releasing hormone agonist and cyclical hormone replacement therapy for dysfunctional uterine bleeding
E. J. Thomas, K. J. Okuda & N. M. Thomas
- 1160 Second trimester amniotic fluid oestriol, dehydroepiandrosterone sulphate, and human chorionic gonadotrophin levels in Down's syndrome
H. S. Cuckle, N. J. Wald, J. W. Densem, J. Canuck & K. B. Abell
- 1163 Relations between the fetal circulation and pituitary-thyroid function
J. G. Thorpe-Beeston, K. H. Nicolaides, R. J. M. Snijders, C. V. Felton, S. Vyas & S. Campbell
- 1168 Patient acceptability of laser and cold coagulation therapy for pre-malignant disease of the uterine cervix
J. D. S. Goodman & D. Sumner
- 1172 Changes in flow velocity waveforms in umbilical and uterine artery following haemodialysis. Case report
Z. Weiner, I. Thaler, N. Ronen & J. M. Brandes
- 1174 Short communications
Epidural analgesia—a cause of transient impairment of the utero-placental circulation?
K. S. J. Oláh & H. Gee
The flying squad—an expensive and potentially dangerous practice in modern obstetrics
A. K. Trehan & I. L. C. Fergusson
Absence of diurnal variation in urinary chorionic gonadotrophin excretion at 8–13 weeks gestation
A. Kent, M. J. Kitau & T. Chard
The effects of pregnancy on previous incontinence surgery. Case report
A. Cumer, L. D. Cardozo & B. G. Wise
Colpo-needle suspension for the treatment of urinary stress incontinence—a new surgical technique
E. Caspi & R. Langer
- 1185 Correspondence
- 1189 Book reviews
- 1192 Erratum

Vol 98 No 12 December 1991

- 1193 Commentaries
Health after childbirth
C. MacArthur, M. Lewis & E. G. Knox
The Robertson-Brosens-Dixon hypothesis: evidence for the role of haemochorial placentation in pregnancy
T. Y. Khong
Elective section after two sections—where's the evidence?
L. J. Roberts
Abortion in Poland
Z. Szawarski
- 1205 Erythrocyte hydration in normal human pregnancy
S. Macphail, T. H. Thomas, R. Wilkinson, W. Dunlop & J. M. Davison
- 1212 Insufficient remodelling of the uterine connective tissue in women with protracted labour
L. Granström, G. Ekman & A. Malmström
- 1217 Fast-scan magnetic resonance imaging of fetal anomalies
A. S. Garden, A. M. Weindling, R. D. Griffiths & P. A. Martyn
- 1223 Fetal heart rate and intrauterine growth
S. M. Robinson, T. Wheeler, M. C. Hayes, D. J. P. Barker & C. Osmond
- 1228 Chromosome abnormalities detected in chorionic villus biopsies of failing pregnancies in a subfertile population
A. M. Lower, M. J. Mulcahy & J. L. Yovich

- 1234 Emergency cervical cerclage
J. MacDougall & N. Siddle
- 1239 Platelet reactivity and serum thromboxane B₂ production in whole blood in gestational hypertension and pre-eclampsia
K. A. Loudon, F. Broughton Pipkin, S. Heptinstall, S. C. Fox, J. R. A. Muchell & E. M. Symonds
- 1245 Is oral contraceptive use still associated with an increased risk of fatal myocardial infarction? Report of a case-control study
M. Thorogood, J. Mann, M. Murphy & M. Vessey
- 1254 Conservative laparoscopic treatment of ectopic pregnancies using the CO₂-laser
P. R. Koninckx, K. Witters, J. Brosens, N. Stemers, D. Oosterlynck & C. Meuleman
- 1260 The role of *Chlamydia trachomatis* and *Neisseria gonorrhoeae* in the aetiology of ectopic pregnancy in Gabon
Y. Ville, M. Leruez, E. Glowaczower, J. N. Robertson & M. E. Ward
- 1267 An audit of the management of ectopic pregnancy
S. G. Norman
- 1273 Colposcopically directed punch biopsy: a potentially misleading investigation
E. J. Buxton, D. M. Luesley, M. I. Shafi & M. Rollason
- 1277 Presence of an oestradiol receptor-related protein in the skin: changes during the normal menstrual cycle
D. Fraser, M. L. Padwick, M. Whitehead, A. Coffey & R. J. B. King
- 1283 Assessment of urinary symptoms in early pregnancy
A. Cutner, L. D. Cardozo & C. J. Benness
- 1287 Sensory urgency: how full is your bladder?
S. M. Creighton, J. M. Pearce, I. Robson, K. Wang & S. L. Stanton
- 1290 Pregnancy in Crigler-Najjar syndrome. Case report
W. G. Taylor, S. A. Walkinshaw, R. G. Farquharson, R. A. Fiskin & I. T. Guilmore
- 1292 Maternal trauma and cerebral lesions in preterm infants. Case reports
D. G. Murdoch Eaton, Y. Ahmed & L. M. S. Dubowitz
- 1295 Retention of the second twin: a viable option? Case reports
M. G. Long, D. M. F. Gibb, S. Kempley, L. D. Cardozo, K. Nicolaidis & H. Gamsu
- 1300 Twin pregnancy in a patient with idiopathic long QT syndrome. Case report
C. Wilkinson, R. Gyaneshwar & C. McCusker
- 1303 Short communication
Avicenna's recipe for contraception
B. Nathan & M. Mikhail
- 1304 Blair Bell Research Society
- 1309 Correspondence
- 1317 Book reviews
- 1320 Author index
- 1333 Subject index
- 1344 Referees 1991

CIBA

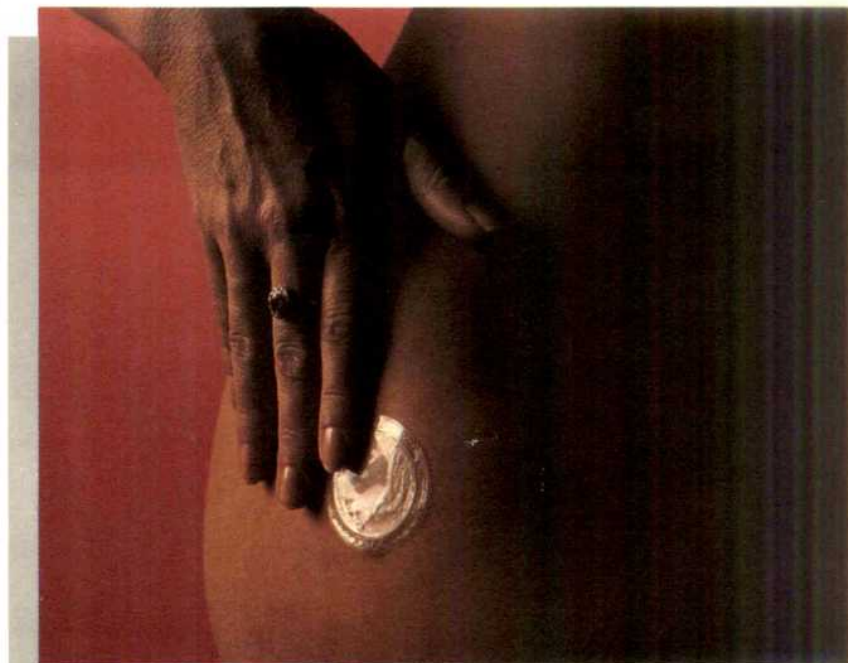
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Vol 98 No 12 December 1991

CONTENTS

- 1193 Commentaries
 - Health after childbirth
C. MacArthur, M. Lewis & E. G. Knox
 - The Robertson-Brosens-Dixon hypothesis: evidence for the role of haemochorial placentation in pregnancy
T. Y. Khong
 - Elective section after two sections—where's the evidence?
L. J. Roberts
 - Abortion in Poland
Z. Szawarski
- 1205 Erythrocyte hydration in normal human pregnancy
S. Macphail, T. H. Thomas, R. Wilkinson, W. Dunlop & J. M. Davison
- 1212 Insufficient remodelling of the uterine connective tissue in women with protracted labour
L. Granström, G. Ekman & A. Malmström
- 1217 Fast-scan magnetic resonance imaging of fetal anomalies
A. S. Garden, A. M. Weindling, R. D. Griffiths & P. A. Martin
- 1223 Fetal heart rate and intrauterine growth
S. M. Robinson, T. Wheeler, M. C. Hayes, D. J. P. Barker & C. Osmond
- 1228 Chromosome abnormalities detected in chorionic villus biopsies of failing pregnancies in a subfertile population
A. M. Lower, M. J. Mulcahy & J. L. Yovich
- 1234 Emergency cervical cerclage
J. MacDougall & N. Siddle
- 1239 Platelet reactivity and serum thromboxane B₂ production in whole blood in gestational hypertension and pre-eclampsia
K. A. Loudon, F. Broughton Pipkin, S. Heptinstall, S. C. Fox, J. R. A. Mitchell & E. M. Symonds
- 1245 Is oral contraceptive use still associated with an increased risk of fatal myocardial infarction? Report of a case-control study
M. Thorogood, J. Mann, M. Murphy & M. Vessey
- 1254 Conservative laparoscopic treatment of ectopic pregnancies using the CO₂-laser
P. R. Koninckx, K. Witters, J. Brosens, N. Siemers, D. Oosterlynck & C. Meuleman
- 1260 The role of *Chlamydia trachomatis* and *Neisseria gonorrhoeae* in the aetiology of ectopic pregnancy in Gabon
Y. Ville, M. Leruez, E. Glowaczower, J. N. Robertson & M. E. Ward
- 1267 An audit of the management of ectopic pregnancy
S. G. Norman
- 1273 Colposcopically directed punch biopsy: a potentially misleading investigation
E. J. Buxton, D. M. Luesley, M. I. Shafi & M. Rollason
- 1277 Presence of an oestradiol receptor-related protein in the skin: changes during the normal menstrual cycle
D. Fraser, M. L. Padwick, M. Whitehead, A. Coffey & R. J. B. King
- 1283 Assessment of urinary symptoms in early pregnancy
A. Cutner, L. D. Cardozo & C. J. Benness
- 1287 Sensory urgency: how full is your bladder?
S. M. Creighton, J. M. Pearce, I. Robson, K. Wang & S. L. Stanton
- 1290 Pregnancy in Crigler-Najjar syndrome. Case report
W. G. Taylor, S. A. Walkinshaw, R. G. Farquharson, R. A. Fiskin & I. T. Gilmore
- 1292 Maternal trauma and cerebral lesions in preterm infants. Case reports
D. G. Murdoch Eaton, Y. Ahmed & L. M. S. Dubowitz
- 1295 Retention of the second twin: a viable option? Case reports
M. G. Long, D. M. F. Gibb, S. Kempley, L. D. Cardozo, K. Nicolaidis & H. Gamsu
- 1300 Twin pregnancy in a patient with idiopathic long QT syndrome. Case report
C. Wilkinson, R. Gyaneshwar & C. McCusker
- 1303 Short communication
Avicenna's recipe for contraception
B. Nathan & M. Mikhail
- 1304 Blair Bell Research Society
- 1309 Correspondence
- 1317 Book reviews
- 1320 Author index
- 1333 Subject index
- 1344 Referees 1991

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